# Quantifying Effects of Spinal Cord Stimulation in Chronic Regional Pain Syndrome Patients

Eline Annemarie van Lange

A thesis submitted to
Delft University of Technology,
Erasmus University Rotterdam
and Leiden University

In partial fulfilment of the
requirements for the degree of

MSc. in Technical Medicine
Track Sensing & Stimulation

02-12-2022

Universiteit Leiden

TU Delft Delft University of Technology

Erasmus Universiteit Rotterdam

This page is intentionally left blank

# QUANTIFYING EFFECTS OF SPINAL CORD STIMULATION IN CHRONIC REGIONAL PAIN SYNDROME PATIENTS

Eline van Lange
Student number: 4390210
01-12-2022

Thesis in partial fulfillment of the requirements for the joint degree of Master of Science in

*Technical Medicine*

Leiden University; Delft University of Technology; Erasmus University Rotterdam

Master thesis project (TM30004 ; 35 ECTS)

Dept. of Biomechanical Engineering, TUDELFT
November 2019 – June 2020
Supervisor(s):
Dr. ir. Cecile de Vos
Prof. Dr. Frank Huygen
Dr. ir. Martijn Starmans

Thesis committee members:
Prof. Dr. ir. Alfred Schouten, TU Delft (chair)
Dr. ir. Cecile de Vos, EMC
Prof. Dr. Frank Huygen, EMC
Dr. ir. Martijn Starmans, EMC



Universiteit Leiden
TU Delft Delft University of Technology
ERASMUS UNIVERSITEIT ROTTERDAM

This page is intentionally left blank

# Summary

**Background**: Complex regional pain syndrome (CRPS) is a clinical disorder characterized by continuous, disproportionate pain and sensory, vasomotor, sudomotor and motor trophic changes. CRPS patients have a heterogeneous clinical picture caused by multiple underlying pathophysiology mechanisms including inflammation, vasomotor disturbances and central nervous system (CNS) dysregulation. Spinal cord stimulation (SCS) is believed to target multiple CRPS mechanisms by stimulating the dorsal column in the spinal cord. Closed-loop SCS is a recently developed form of SCS in which the stimulation intensity adapts to the patient's position, continuously stimulating the same amount of fibers in the dorsal column. This constant perceived stimulation intensity may benefit CRPS patients who are generally hypersensitive.

**Objectives**: To better understand the effects SCS has on the CRPS mechanisms, my research focuses on quantifying changes in vasomotor disturbances due to conventional SCS treatment using thermographic image analysis. In addition, exploratory analysis is performed in patients treated with closed-loop SCS to evaluate its effects on CRPS mechanisms.

**Method:** Various histogram features indicating temperature intensity were selected based on histogram distributions of the thermographic images. These features were then extracted from the affected and unaffected extremities of each image. The histogram features of patients with and without vasomotor improvement were compared based on the change in differences between affected and unaffected extremities after 3 months of SCS. The change between improved or not improved was then determined for different characteristics of the patients, such as affected extremity and CRPS type. It was hypothesized that with improved vasomotor symptoms, the affected and unaffected extremities would become more similar and thus the difference would become smaller.
For evaluation of the effects of closed-loop SCS on CPRS mechanisms, measurements were conducted before implantation and up to 6 months of follow-up. Measurements include thermographic images, CRPS severity score (CSS), Condition Pain Modulation (CPM), Temporal Summation (TS) and determination of sIL-2R levels using blood samples. In addition, conventional SCS was compared to closed-loop SCS, with patients randomized to receive both settings during the follow-up for two months.

**Results:** The following histogram features were selected: mean, median, minimum, maximum, peak, skewness, kurtosis, and quartile range. Based on 28 patients, for patients with improved vasomotor symptoms a decrease in difference was observed for histogram features mean, median, minimum, peak and quartile range. Furthermore, statistically significant differences were found in patients with vasomotor symptoms at baseline compared to patients without vasomotor symptoms for the mean ($p=0.026$), median ($p=0.046$), minimum ($p=0.008$), and quartile range ($p=0.016$). For patients with a cold CRPS type, statistically significant different feature values were observed between patients with and without vasomotor improvement in maximum ($p=0.024$), peak ($p=0.016$), and quartile range ($p=0.027$), with a decrease of histogram feature values. No statistically significant differences were found between the affected upper or lower extremities.
Four patients with a closed-loop SCS system had their 3-month visit, of which 2 also had their 6 month follow-up. In three patients, the reduction of vasomotor symptoms corresponded to a reduction of histogram feature values and an improvement in pain scores. In addition, three patients completed randomization, and all three preferred the closed-loop SCS over conventional SCS.

**Conclusion:** After three months of SCS, patients with improved vasomotor symptoms show slight decreases in five histogram features on improved vasomotor disturbances quantified with thermographic images. This shows that the use of thermographic images is a promising method for the quantification of vasomotor disturbances. However, more patients should be included in the analysis.
When evaluating the effects of closed-loop SCS on CRPS mechanisms, SCS improved the vasomotor disturbances, CNS dysregulation, and activity of three included patients. All three patients preferred closed-loop SCS.

This page is intentionally left blank

# Acknowledgment

During an intensive period of 10 months, I wrote a thesis about my research on the effects of spinal cord stimulation in patients with complex regional pain syndrome. I did not do this on my own. Therefore, I would like to express my sincere appreciation to my supervisors, Cecile de Vos, Martijn Starmans and professor Frank Huygen for their contributions and continuous support during the research and writing my thesis.

First of all, I would like to thank Cecile for the daily guidance on a technical, academic and personal level. With your enthusiastic, cooperative and open approach, I experienced our conversations as pleasant and instructive. You asked many questions and sometimes made it challenging for me to make sure I thought things through. I sincerely hope you also enjoyed the moments when we could blow off steam together during our lengthy conversations. Martijn, thank you for taking the time to project your extensive knowledge about radiomics, as it was a new topic for me. You helped me a lot by providing more information, patiently explaining everything and influencing my view of things, especially when I had to take a completely different approach. Additionally, I would like to thank my clinical supervisor Frank for your knowledge and helpful comments on pain medicine. Above all, I am grateful for your trust in me to coordinate a clinical trial. I learned very much from this experience and it helped me evolve as a clinical professional. Furthermore, I would like to thank all my colleagues at the Center for Pain Medicine at Erasmus MC for your openness and welcoming me into your daily clinical tasks. I enjoyed feeling like I became one of you over the course of the 14 months I have worked with you. Thank you for all the input, which has taught me so much about the interaction with patients, pain medicine and neuromodulators, and of course during the lunch talks for some well-deserved distractions. I look forward to celebrating the end of my thesis with you soon.

My biggest thanks go to my loving friends and family who have supported me throughout the entire process. You gave me plenty of moments to blow off steam but also time to focus on myself. Finally, I would like to say a special thank you to my mother, who took the time to review my writing.

Rotterdam, December 2022 Eline van Lange

This page is intentionally left blank

# Table of Contents

# Abbreviations

| | |
|---|---|
| ANS | Autonomic Nervous System |
| BL | Baseline visit CL-study |
| CL | Closed Loop |
| CL-study | Closed Loop Study |
| CPM | Conditioned Pain Modulation |
| CNS | Central Nervous System |
| CRPS | Complex Regional Pain Syndrome |
| CSS | CRPS severity score |
| ECAPs | Evoked Compound Action Potentials |
| FR-study | Frequency study |
| G0 | Baseline visit FR-study |
| G1 | Three months visit FR-study |
| IPG | Implantable Pulse Generator |
| NRS | Numerical Rating Scale |
| OL | Open Loop |
| QST | Quantitative sensory test |
| SCS | Spinal Cord Stimulation |
| sIL-2R | Soluble IL-2 receptor |
| T0 | Permanent implantation CL-study |
| TS | Temporal Summation |
| WORC | Workflow for Optimal Radiomics Classification |

# 1 Introduction

Complex regional pain syndrome (CRPS) is a clinical disorder characterized by continuous, disproportionate pain and sensory, vasomotor, sudomotor and motor trophic changes, usually in the distal part of an extremity. CRPS often causes severe limitations in daily activities and functions (1–4). The exact pathophysiology of CRPS is still unknown, but there is increasing evidence that multiple underlying pathophysiologic mechanisms, both peripheral and central, cause a heterogeneous clinical picture of CRPS patients (1,5). The mechanisms include inflammation, vasomotor disturbances and Central Nervous System (CNS) dysregulation (1,6,7). They influence and maintain each other, making CRPS a self-perpetuating syndrome.

The treatment of CRPS aims to reduce pain and improve the affected extremities' functions (8). Eventually, neuromodulation, such as spinal cord stimulation (SCS), is often considered when conventional therapies, such as medication, do not have the desired effect (9,10). With SCS, the dorsal column in the spinal cord is stimulated by electrical pulses. SCS can target multiple CRPS mechanisms simultaneously and is a proven effective treatment for CRPS patients by reducing pain and improving patients' blood flow, general functioning, and quality of life (10–13).

With a recently developed type of SCS, closed-loop SCS, the intensity of the stimulation adapts to the patients' postures. Because CRPS patients are often hypersensitive to somatosensory stimuli due to CNS dysregulation, closed-loop stimulation could improve SCS treatment for CRPS patients by administering stimulation pulses with a controlled amplitude and, therefore, a more constant stimulated amount of fibers in the dorsal column (14).

## 1.1 Objectives

More extensive knowledge of the SCS effects per CRPS mechanism could contribute to a better understanding of the effects of SCS on CRPS and of closed-loop SCS in particular. This could ultimately improve the treatment of CRPS patients. To this end, the results of various measurements obtained from CRPS patients treated with SCS are analyzed to distinguish the CPRS mechanisms.

The Center for Pain Medicine at Erasmus MC visually assesses thermographic images showing the skin's temperature distribution to detect vasomotor disturbances, in addition to physical examination. My research aims to investigate the relationship between quantitative features of thermographic images and the changes in vasomotor disturbances using radiomics. For this purpose, a dataset with CRPS patients who have had conventional SCS, i.e., without the closed-loop system, is used.

Subsequently, an exploratory analysis is performed in patients with closed-loop SCS to evaluate the effects of SCS on vasomotor disturbances, CNS dysregulation, inflammation and the activity of the patients. Based on case reports, the results of quantifying the thermographic images and other measurements are analyzed. The other measurements include CRPS severity score (CSS), Condition Pain Modulation (CPM), Temporal Summation (TS), determination of sIL-2R levels using blood samples and tracking the number of steps for activity. In addition, conventional SCS is compared to closed-loop SCS.

More information about the CRPS mechanisms, SCS, and the different measurements can be found in chapter *2 Background*.

# 2
# Background

## 2.1 CRPS Mechanisms

The pathological mechanisms of CRPS vary from patient to patient but often develop in a specific sequence after the onset of injury into inflammatory, vasomotor disturbances, and, ultimately, CNS dysregulation.

The inflammatory reaction to tissue damage is exaggerated in CRPS patients, involving two inflammatory cascades; classical inflammation and neurogenic inflammation. During these cascades, neurotransmitters, neuropeptides, antibodies and cytokines are released from the peripheral afferent sensory neurons and cause an imbalance in the peripheral part of the affected extremity and the spine (3,15,16).

With vasomotor disturbances, microvascular damage is caused by neurogenic inflammation, endothelial dysfunction, and a dysregulation of the Autonomic Nervous System (ANS). This damage results in vasomotor disturbances, including temperature and color differences of the affected body part (17–19).

CRPS patients may develop CNS dysregulation in response to continuous noxious stimuli at the spinal or supraspinal level. This causes central sensitization, disinhibition of sensory fibers, and cortical reorganization. CNS dysregulation can result in the development of pathological nociception, which causes hyperalgesia and allodynia, somatosensory disturbances, and can eventually lead to persistent vasomotor and motor disturbances (3,6,20). CNS dysregulation will primarily lead to the maintenance of chronic pain and CRPS itself (7).

## 2.2 Spinal Cord Stimulation

There are different types of SCS. With conventional SCS, electrical stimulation is applied to the dorsal column of the spinal cord. Stimulation originates from a lead with electrodes placed in the epidural space and coupled to an implantable pulse generator (IPG) see **Figure 1** (21). The lead is located around the midline of the dorsal column and primarily stimulates the Aβ fibers (22–24). Through stimulation of these fibers, SCS treats the symptoms of CRPS by engaging multiple mechanisms via spinal and supraspinal pathways see **Figure 2**. For example, it is assumed that, at the spinal level, antidromic activation of the Aβ fibers causes inhibition of central sensitization in the dorsal horn. In contrast, orthodromic activation of the Aβ fibers activates the descending inhibitory pathway at supraspinal level.

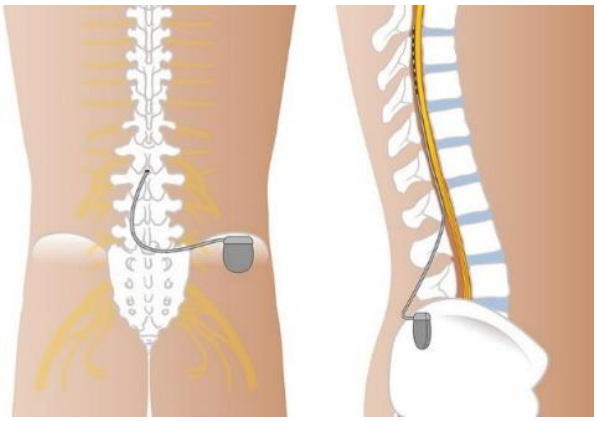

***Figure 1**. Location of SCS*
*A lead with electrodes is placed in the spinal cord's epidural space around the dorsal columns' midline. The lead is attached to an IPG, which is placed near the hips.*
*Adapted from Lundeland 2021 (21)*

## 2.3 Closed-Loop SCS

Closed-loop stimulation is a variation of conventional SCS and also stimulates the Aβ fibers in the dorsal column. With closed-loop stimulation, the electrodes on the lead measure the activated fibers in the dorsal column, which are the evoked compound action potentials (ECAPs). A feedback system adjusts the stimulation amplitude (mA) to keep the intensity of the activated fibers consistent and thus maintain a stable ECAP value (14,25).

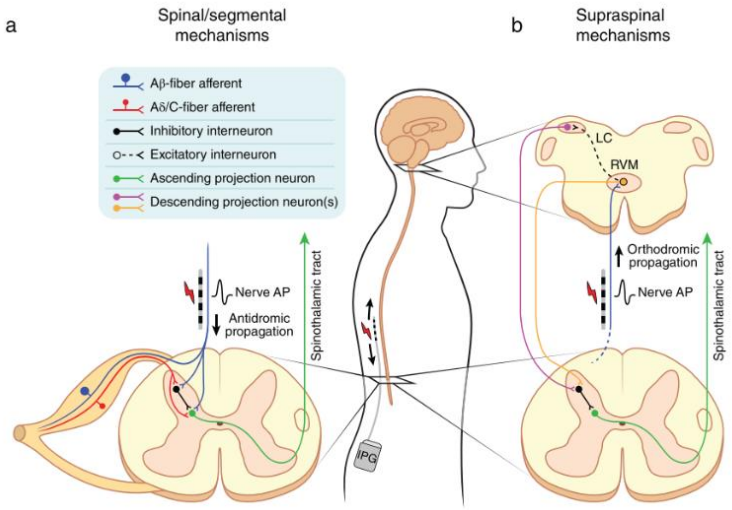


***Figure 2**. Effects of SCS on the spinal and supraspinal levels.*

***a**. At the spinal level, SCS affects the antidromic propagation of the Aβ fibers, inhibiting the interneurons that transmit noxious stimuli in the dorsal horn.*

***b.** At the supraspinal level, SCS ensures the orthodromic propagation of the Aβ fibers, activating the descending inhibitory pathway.*

*Adapted from Sankarasubramanian (36)*

## 2.4 Effects of SCS on CRPS Mechanisms

The knowledge of the effects of SCS on the mechanisms of CRPS is mainly based on research on conventional SCS. Presumably, the main impact of conventional SCS is improving CNS dysregulation by counteracting central sensitization in the dorsal horn and influencing the cortical reorganization that occurs in CRPS. This mainly leads to improved pain processing, reducing pain, allodynia, and hyperalgesia (6,13,24).

SCS also directly affects vasomotor disturbances and inflammation in CRPS patients, improving symptoms, such as sudo- and vasomotor function. However, the effect of SCS on inflammation and vasomotor disturbances in CRPS could also be an indirect effect due to the influence of improved CNS dysregulation. Thus, it is sometimes unclear how much of the effect is a direct response to SCS treatment or a reaction to ameliorating CNS dysregulation when determining the effects on these two mechanisms (6,7,26,27).

## 2.5 Assessment of the Mechanisms of CRPS

Several tests and measurements can be performed to assess the effect of SCS on different mechanisms of CRPS. Because the mechanisms are intertwined, symptoms can often be caused by more than one mechanism. Therefore, the results of some tests will provide a general impression of changes in the patient's CRPS symptoms and thus provide information on multiple mechanisms at once, with potentially limited information about the effect on the individual mechanism. The following tests are examples used to evaluate the effect of SCS on the CRPS mechanisms.

### 2.5.1 Assessment of vasomotor disturbances

To investigate the effect of SCS on vasomotor disturbances, the blood flow and microcirculation of the affected body part should be examined. For my research, vasomotor symptoms were assessed with anamnesis and physical examination, as well as by determining the skin temperature distribution on the surface of the extremities using thermographic images, see **Figure 3**.

Thermographic images can measure skin temperature through infrared radiation (28). With CRPS patients, the skin temperature is often asymmetrical between the affected and unaffected sides. At Erasmus MC, the thermographic images are assessed visually, and there is no standard interpretation of the images to determine the effect of SCS on vasomotor disturbances.

My research, therefore, examined whether the images can be quantitatively assessed based on medical imaging features. Using radiomics, medical image features were extracted with Python's open-source Workflow for Optimal Radiomics Classification (WORC) software (29–32). The features were determined per left and right extremity, which required segmentation of the thermographic images to extract the region of interest, i.e., each side. Segmentations were obtained using a U-net model described in the study by Mostert et al. (2020) (33). The U-net model is a convolutional neural network trained by Mostert et al. (2020) to predict a mask of the extremities.

With Radiomics, 564 features are calculated per extremity, including 13 histogram features indicating the images' intensity, thus representing temperature distributions in the thermographic images. In addition, shape and texture features are also determined, but a recent study by Bijl et al. showed that CRPS patients could be distinguished from healthy people based on only histogram features (34). Therefore, in my research, I only determined the histogram features, which are statistical calculations of the histograms and consist of; the mean, median, standard deviation, minimum, maximum, skewness, kurtosis, peak, peak position, range, energy, quartile range and entropy.

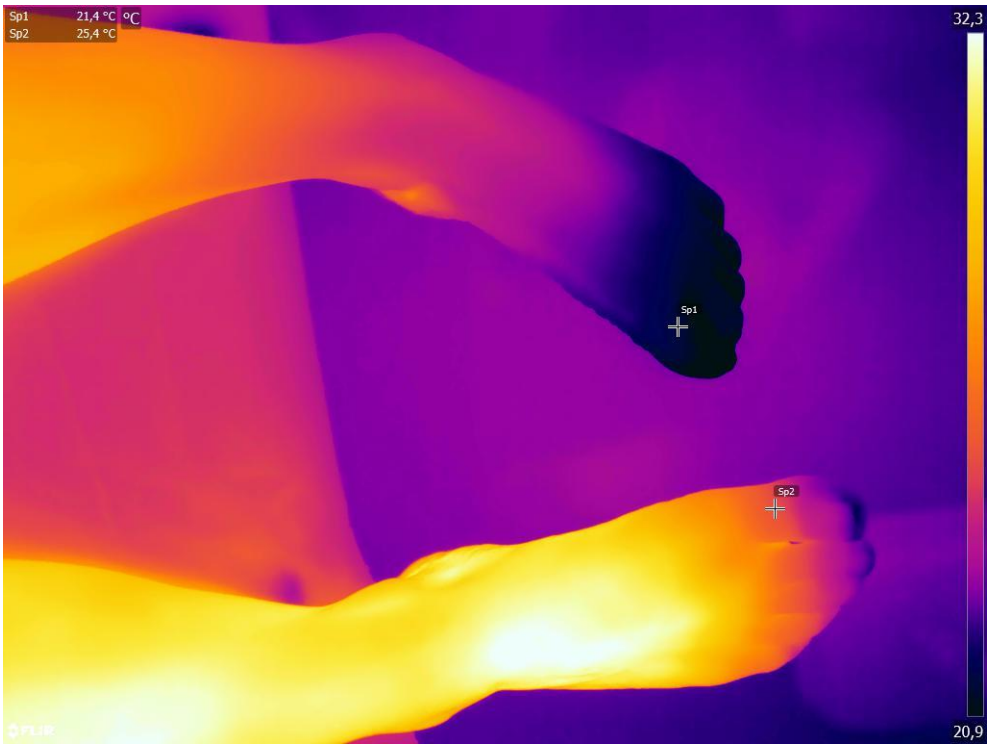


***Figure 3**. Thermographic image of a patient with CRPS of her left foot. The image was taken before the SCS treatment, with the FLIR-T1010 camera, and shows a temperature difference of 4 °C between affected (Sp1) and unaffected (Sp2)*

### 2.5.2 Assessment of CNS dysregulation

To assess the effect on central sensitization and pain processing dysregulation that occurs as a result of CNS dysregulation, a quantitative sensory test (QST) could be performed. QST is used to assess somatosensory processing and, thereby, the possible analgesic effect of SCS (35,36).

For my research, Temporal summation (TS) and conditioned pain modulation (CPM) were performed on the CRPS patients, which are dynamic QST tests. The increased pain response due to repeated noxious stimuli is examined with TS. An elevated TS result in chronic pain patients may correlate with spinal-level central sensitization (37). With CPM, the supraspinal pain inhibitory pathway is evaluated by the inhibition of a first noxious stimulus by applying a second noxious stimulus. Studies found that this effect is diminished in chronic patients leading to less inhibition of the first stimulus (6,36,38). However, Kriek et al. (2022) found an efficient CPM effect in a group of 31 CRPS patients, both before and a second noxious stimulus of ice water, indicating that pain thresholds are not affected by the pain perception of the ice water (39).

### 2.5.3 Assessment of inflammation

To determine the inflammatory response in CRPS patients, the values of the released particles indicative of inflammation, such as neurotransmitters, cytokines, etc., can be monitored. Ideally, these values should be obtained from the affected extremity and spine as they are released here. However, a less invasive manner was chosen for my research to detect inflammation, using an indirect approach by measuring the soluble IL-2 receptor (sIL-2R) from blood samples (40).

### 2.5.4 Overall assessment of CRPS symptoms

The CRPS Severity Score (CSS) is a questionnaire administered to CRPS patients to monitor the patient's changes in signs and symptoms of CRPS through questions and physical examination (41). It provides information about the various mechanisms and symptoms of the patient, often related to their general health and functioning. For example, the numerical rating scale (NRS) pain score is requested with the CSS, where the pain is scored between 0, no pain, and 10, unbearable pain. Furthermore, symptoms associated with CNS dysregulation, i.e., pain processing, are questioned, such as hyperalgesia and allodynia, as well as symptoms related to sudomotor, vasomotor, and motor disturbances.

# 3 Method

My research consists of two parts. First, I investigated the possibility of quantifying the thermographic images in section 3.1. Data from a previous study from the Center for Pain Medicine at Erasmus MC were used for this purpose. In this study, CRPS patients had received conventional SCS for a minimum of three months after implantation, this study is referred to as the frequency study (FR-study).

Secondly, I evaluated the effects of SCS on vasomotor disturbances, CNS dysregulation, inflammation and activity of CRPS patients receiving closed-loop SCS in section 3.2. For this evaluation, data from an ongoing exploratory study at the Center for Pain Medicine at Erasmus MC, referred to as the closed-loop study (CL study), were used.

## 3.1 Analyses of thermographic images based on the frequency study

The thermographic images were analyzed to quantify the effect of SCS on the potential improvement of vasomotor disturbances in CRPS patients from the FR-study. With the use of radiomics, histogram features were determined.

A difference in temperature distribution between affected and unaffected extremities at baseline was expected. It was hypothesized that when there is an improvement in vasomotor symptoms, the difference between the affected and unaffected histogram features will decrease after 3 months of SCS. These decreased histogram feature values meant a reduced temperature difference between the affected and unaffected sides. As the temperature of the skin surface is an indirect measure of the vasomotor function in the extremity, a reduced temperature difference between the affected and unaffected sides after SCS would be related to improved vasomotor disturbances.

The changes per histogram feature were examined to test the hypothesis and to assess whether the thermographic images could be quantified based on the histogram features. To this end, it was first determined which histogram features would be included based on the histograms of the thermographic images. Subsequently, the distributions of the feature values were examined between baseline and 3 months SCS. Finally, changes and possible decreases of difference between affected and unaffected extremities after 3 months of SCS were evaluated per feature, considering different characteristics of CRPS patients.

### 3.1.1 Data acquisition frequency study

For the FR-study, patients with CRPS received conventional SCS for three months after permanent implantation (42,43). The data from the study include documentation of anamnesis, including the NRS score, physical examination, CPM measurements and thermographic images of both the left and right side of the affected extremity. For each patient, data were obtained at baseline (G0) and 3 months after permanent implantation (G1).

### 3.1.2 Preprocessing

Before using radiomics for feature extraction, several processing steps were performed with the images. It was essential that the left and right parts for each affected extremity were available and that the images were rotated so that the toes and fingers were always pointing upwards.

After preprocessing the data, the images were segmented to extract the regions of interest, i.e., the left and right extremities, using the trained U-net model of Mostert et al. (2020). Subsequently, the mask was split to obtain both a left and a right part. If necessary, the masks were corrected manually.

### 3.1.3 Histogram feature extraction

The histogram features were extracted for each left and right extremity using radiomics and the WORC software. These extracted histogram features were ultimately used to investigate the relationship between quantitative features of thermographic images and changes in vasomotor disturbances after three months of SCS. **Figure 4** shows an example of the segmented left and right side with the corresponding histograms of a patient from the FR-study.

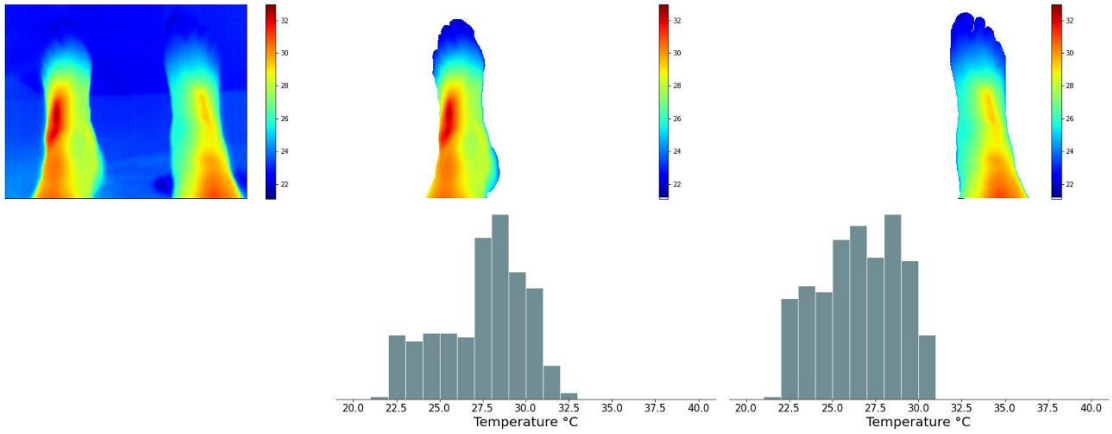


***Figure 4**. Thermographic image of patient 13 from the FR-study. The left and right sides are separated in the corresponding histogram below the images. The histograms indicate how often the temperatures appear in the image. With a higher bar corresponding to more frequent points of the respective temperature.*

### 3.1.4 Interpretation of thermographic images and histograms

All thermographic images and associated histograms were visually analyzed to determine how the data could be used to assess the effect of SCS on vasomotor symptoms. The main focus was on which patterns in the images' histograms were related to vasomotor symptoms.

To this end, the images and histograms were evaluated to assess which characteristics were associated with vasomotor symptoms. Therefore, based on the differences between the histograms and thermographic images of the affected and unaffected sides of the patients, histogram features were selected for the remainder of my research.

### 3.1.5 Determining the difference between affected and unaffected sides

To determine the difference between the affected and unaffected sides, I decided not to distinguish which side was affected. Therefore, the absolute difference between the left and right extremities is determined for each selected histogram feature value for G0 and G1. Then, to determine the change in histogram feature values after 3 months of SCS, the differences at G0 and G1 were subtracted, see Equation 1.

$$f(x) = |L_{ext} - R_{ext}|_{G1} - |L_{ext} - R_{ext}|_{G0} \qquad \textit{Equation 1}$$

### 3.1.6 Reduction after three months of SCS for all patients

The selected histogram features were analyzed at both measurement moments, G0 and G1, and subsequently, the change between the measurement moments was evaluated, for all patients. To this end, the absolute difference between the left and right extremities was determined for each selected histogram feature at G0 and G1. Then the values of G0 were compared and subtracted from the absolute difference between the left and right extremities at G1, see Equation 1. We assumed that if SCS affected and improved vasomotor disturbances, a decrease in the histogram feature values between G0 and G1 was expected.

### 3.1.7 Reduction after three months of SCS for patients with vasomotor improvement

To assess whether the selected histogram features could determine patients' vasomotor improvement, a distinction was made between patients with or without improvement in vasomotor symptoms after 3 months of SCS. The presence or absence of vasomotor improvement was based on both the physician and patient's findings from anamnesis and physical examination at G0 and G1.

The vasomotor symptoms assessed by the physician and patients were based on the temperature and skin color change between the affected and unaffected sides. Since both evaluated two symptoms, the maximum score was a 4. A reduction in the score was assumed to be an improvement in vasomotor symptoms.

The patients were then categorized as improved when there was some improvement in vasomotor symptoms and not improved when there was no improvement or even aggravation of vasomotor symptoms. For each selected histogram feature, the change was determined by the absolute difference between left and right at G0 and G1, according to Equation 1. It was expected that the improvement in vasomotor symptoms would result in a reduction between G0 and G1.

The presence or absence of improvement in vasomotor symptoms and the difference in feature values between them were determined for all patients. However, the physician-patient findings did not identify minor changes and only determined any temperature or color differences. Therefore, I also assessed the change in symptoms based on a visual assessment of the thermographic image, where small changes were also seen as improvements in symptoms. These findings were subsequently compared with the physician-patient results.

Furthermore, the improvement based on physician-patient was determined for patients diagnosed with vasomotor symptoms at baseline, between patients with affected upper and lower extremities, and for patients with a warm, cold, or normal (no difference in temperatures) CRPS type, all based on a physical examination by the physician.

### 3.1.8 Statistical analysis

To compare the distribution of features between G0 and G1 for all patients, the Wilcoxon Signed Rank test was used as the data were paired and nonparametric, with a continuity correction applied. A p-value less than 0.05 was considered statistically significant.

A two-tailed Mann-Whitney U test was used or the statistical analysis between patients with and without vasomotor improvement. A p-value of less than 0.05 was considered statistically significant. By default, for groups larger than eight, the test statistics were corrected with the critical value of the Mann-Whitney U test. The statistics were not corrected for groups smaller than eight.

The results were visualized in boxplots. The boxes represent the data between the first quartile (25%) and the third quartile (75%), the interquartile range. The whiskers are elongated out of the box by 1.5 times the interquartile range, while the outlier are values outside of the whiskers.

## 3.2 Measurements from the Closed-Loop study

Based on case reports, the effects of closed-loop SCS on vasomotor disorders, CNS dysregulation, inflammation, and activity were evaluated in patients enrolled in the ongoing exploratory CL-study. Data from CSS, thermographic images, CPM, TS, blood samples, and Fitbit were obtained during visits. CSS results provided an overall picture of CRPS symptoms from the multiple mechanisms. The selected histogram features of the quantification of the thermographic images were used to evaluate the changes in vasomotor disturbances. CPM and TS results were assessed for the effects of SCS on CNS dysregulation. At the same time, patients' inflammation was evaluated with sIL-2R levels using blood samples, and the step count activity was monitored with a Fitbit device. In addition, open-loop SCS, i.e., conventional SCS, was compared to closed-loop SCS.

### 3.2.1 Data acquisition closed-loop study

For the CL-study, CRPS patients received an SCS lead and an Evoke IPG from Saluda Medical after permanent implantation. The patients were followed up to 6 months after permanent implantation with a baseline measurement before the trial, see **Figure 5**. During each visit, the measurements were conducted to evaluate the effects of SCS per mechanism.

The patients received closed-loop stimulation for the first three months. To explore the difference in effect on the CRPS mechanisms between closed-loop SCS and open-loop SCS, the patients in the CL-study also underwent a randomization trajectory in which they received both closed-loop and open-loop SCS each for 1 month. This was done between 3 and 5 months after the permanent implantation. After they had received both settings, the patients could choose which setting they preferred. In addition to the data from the standard measurements, the final choice of SCS type was included as an endpoint. These data can help determine how the closed-loop system works on a patient-by-patient basis compared to conventional SCS.

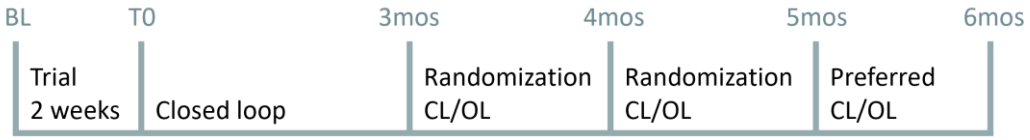


***Figure 5*** *Patient visits in the CL-study.*
*BL is the baseline visit before trial implantation, and T0 is the permanent implantation after the trial period. After T0, the stimulation is turned off for two weeks, and then a closed loop is applied for three months. At the 3-month visit, the randomization process begins, with half of the patients receiving closed-loop, the other half open-loop SCS between the 3rd and 4th months, and the other setting between 4 and 5 months. After the patients have chosen the preferred setting, it is applied in the last month to the end of the study. BL = baseline, T0 = permanent implant, mos = months, CL = closed-loop, OL = open-loop*

### 3.2.2 CRPS severity score

Symptoms from all CRPS mechanisms were obtained with the CSS. The CSS was conducted at each visit. The patient was first asked about the symptoms, then the researcher observed the clinical CRPS symptoms. The questions and the perceived signs are scored with Yes = 1 if present and No = 0 if absent. The total score is the sum of the Yes answers (unweighted) and can range from 0-16, with a higher score indicating greater CRPS severity. The severity score is expected to decrease as SCS will improve CRPS symptoms.

### 3.2.3 Thermographic images of the CL-study

To investigate the improvement in vasomotor symptoms, the resulting histogram features from *3.1* were used to analyze the thermographic images of the CL study patients taken with a FLIR-T1020 camera.

At the beginning of each visit, the thermographic images were taken, and the changes in feature values between the different measurements were observed. Again, the absolute difference between left and right was determined for each measurement moment. Since the FR-study evaluates the effect of 3 months post-implantation SCS, this time point was examined and viewed in the CL-study patients using the assumptions of the FR-study. In addition, the stimulation effects on the changes in features were also investigated up to 6 months after implantation to evaluate the effect of the closed-loop versus open-loop SCS.

### 3.2.4 Conditioned Pain Modulation and Temporal Summation

Results from the CPM and TS were used to evaluate the effect of SCS on CN dysregulation in CRPS patients, as CPM and TS may be able to identify changes in pain processing.

For TS, a 256 mN pinprick was used on the affected and unaffected extremities. First, the unaffected side was tested, and then the affected side, five rounds each. One single and then ten repeated pricks were administered per round, while also obtaining the corresponding NRS score. Based on the requested NRS scores corresponding to single and repetitive pricks, the ratio was calculated per side, and subsequently, the difference between the sides was determined, see Equation 2.

For the CPM, electrocutaneous stimulation was used to determine the pain thresholds before and after an additional noxious stimulus of ice water. A rising current (mA) was given three times, and the patient had to stop the current when the sensation became very painful. Each time an NRS score was requested. This was performed before and after the ice water. The median of each moment was determined with the corresponding NRS score and the difference before and after ice water was calculated, see Equation 3.

With an improved CNS, an elevated TS in pain patients was expected to reduce after SCS, as the affected side was expected to become more similar to the healthy side. With CPM, the ratio after the ice water would be expected to increase as the inhibition pathway improves after SCS, therefore the difference between before and after would decrease.

$$\frac{\bar{x}(5\times\ NRS_{1\ prick})}{\bar{x}(5\times NRS_{10\ pricks})}\ unaffected\ side\ -\frac{\bar{x}(5\times\ NRS_{1\ prick})}{\bar{x}(5\times NRS_{10\ pricks})}\ affected\ side \qquad \textit{Equation 2}$$

$$\frac{Med(3\times current)}{Med(3\times NRS)}\ before\ ice\ water\ -\frac{Med(3\times current)}{Med(3\times NRS)}after\ ice\ water \qquad \textit{Equation 3}$$

### 3.2.5 Inflammatory values

To assess the effect of SCS on the inflammation in the CRPS patient, blood samples were taken to determine the level of sIL-2R. Levels above 555 units per milliliter (U/ml) are considered elevated (40).

### 3.2.6 Activity of CRPS patients

The CRPS patients' activity was monitored through the number of steps measured with a Fitbit device. The mean number of steps was calculated of two weeks before each visit. The hypothesis was that patients would move more after pain and symptoms decreased.

### 3.2.7 Closed-loop SCS and conventional SCS

To explore the difference between closed-loop SCS and open-loop SCS on the effect of CRPS patients, the results of the measurements during the randomization trajectory were analyzed, as well as the patients' preferred SCS setting.

# 4
# Results

## 4.1 Thermographic images FR-study

At least one thermographic image was obtained from 28 patients on both G0 and G1, resulting in 50 thermographic images from which the histogram features were extracted. The calculated differences in left and right extremities between G0 and G1 for all histogram features of the 50 included thermographic images are shown in *Appendix C*. The pre-processing steps have been performed for each thermographic image, an example of a patient's pre-processing and segmentation steps is shown in *Appendix A*.

### 4.1.1 Histogram feature selection

The histogram features were selected based on the thermographic images and associated histograms. When evaluating the histograms, the corresponding distributions of the affected side appeared to be more dispersed. This phenomenon is visible in cold (**Figure 6** and **Figure 7**) and warm CRPS patients (**Figure 8**). At G1, left and right extremity histogram distributions appeared to be more similar in patients with improvement in vasomotor symptoms, consistent with images of affected and unaffected patients being more similar (**Figure 8** and **Figure 9**). In addition, the peak was in 19 of 28 patients with a lower temperature on the affected side, especially in patients with cold CRPS, and less prominent with warmer distributions.

In some images, the area between the left and right sides was captured differently because the limbs were in different positions. For example, in patients with dystonia, see **Figure 9**. Some patients had a warmer temperature distribution even though they were assumed to have cold CRPS, and even between one patient, the change in temperature distribution can differ between moments (**Figure 10**). For my research, it was, therefore, decided not to take into account the additions of temperatures, which are calculated with histogram feature energy, because these depend on the number of measurement points, which can differ between left and right.

The following histogram features were selected to determine whether quantification of the thermographic images is possible to identify changes in vasomotor symptoms, as these features determined magnitudes and changes in dispersion and were not affected by the manner in which the images had been created: 1) The mean and median features, which are determined from all temperature points. 2) The minimum value corresponding to the temperature at 2% of the data. 3) The maximum value, the temperature corresponding to 98% of the data. 4) The peak temperature corresponds to the highest histogram bar, which was the temperature most often occurring. 5) The features skewness and kurtosis look at the tail of the distribution. Skewness looks at the symmetry of the histogram, while kurtosis determines whether the histogram is heavy or light-tailed. 5) Lastly, the quartile range feature was selected, which determines the difference between the temperatures corresponding to 25% and 75% of the histogram data.

### 4.1.2 Comparing histograms of the affected and unaffected sides

For the following subsections, the absolute difference was determined between the left and right sides of the affected extremity for each patient at G0 and G1. **Figure 11** shows the overlapping histograms of the left and right foot of patient 13 at moments G0 and G1, where at G1, the histograms of the affected and unaffected sides are more similar. Therefore, we assumed that the left-right difference between G0 and G1 reduced with the improvement of vasomotor symptoms.

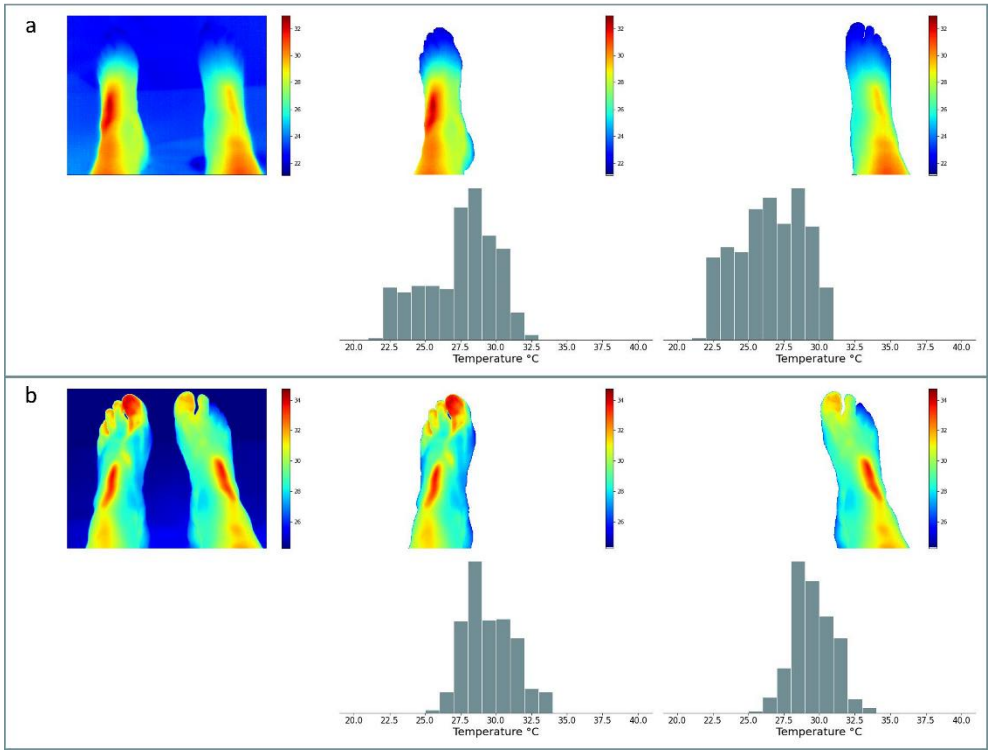


***Figure 6*** *The feet of patient 13*
*The right foot was affected, vasomotor symptoms were present at G0, and without improvement at G1 according to the physician and patient.*
*a. G0, with the right foot affected.*
*b. G1, without improvement, however the distribution seems to be more similar to the left feet.*

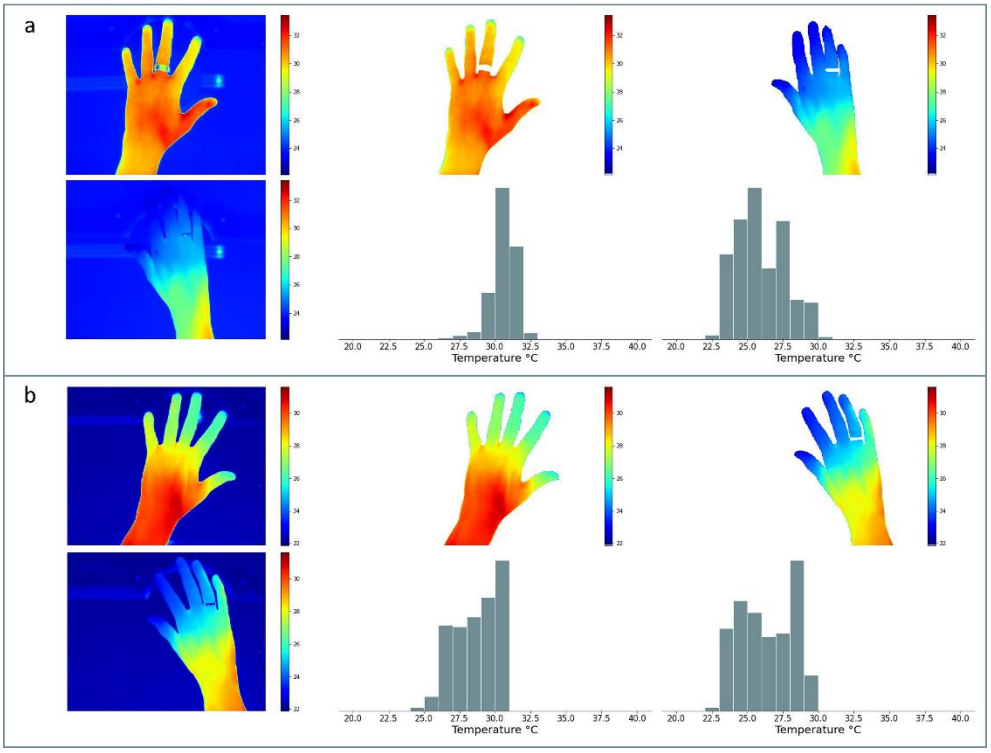


***Figure 7*** *The dorsal hands of patient 36*
*The left hand was affected, vasomotor symptoms were present at G0, and no improvement was established at G1 by the physician and patient*
*a. G0, with the left hand affected.*
*b. G1 without improvement, on the images and histograms, there also appears to be little or no change.*

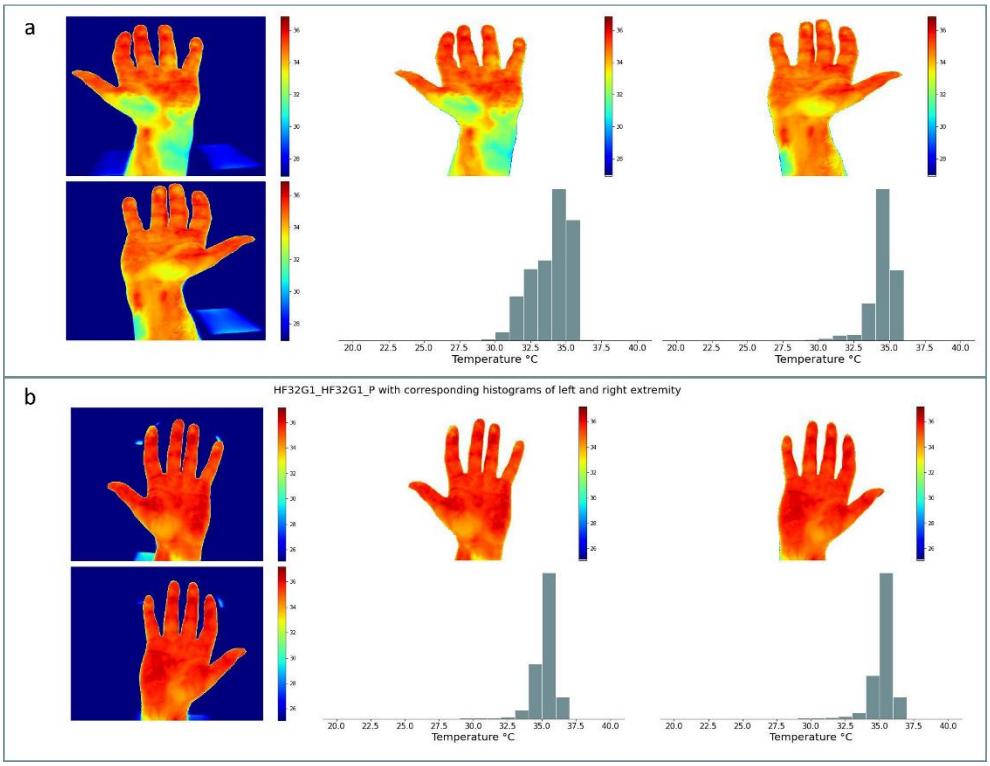


***Figure 8*** *The palmar hands of patient 32*
*The hands are photographed separately, so the left hand is above the image of the right hand.*
*The left hand was affected, vasomotor symptoms were present at G0, and improvement at G1 was established by the physician and patient*
*a. G0, with the left hand affected.*
*b. G1, with improvement, and the temperature distribution seems to be more similar to the right hand.*

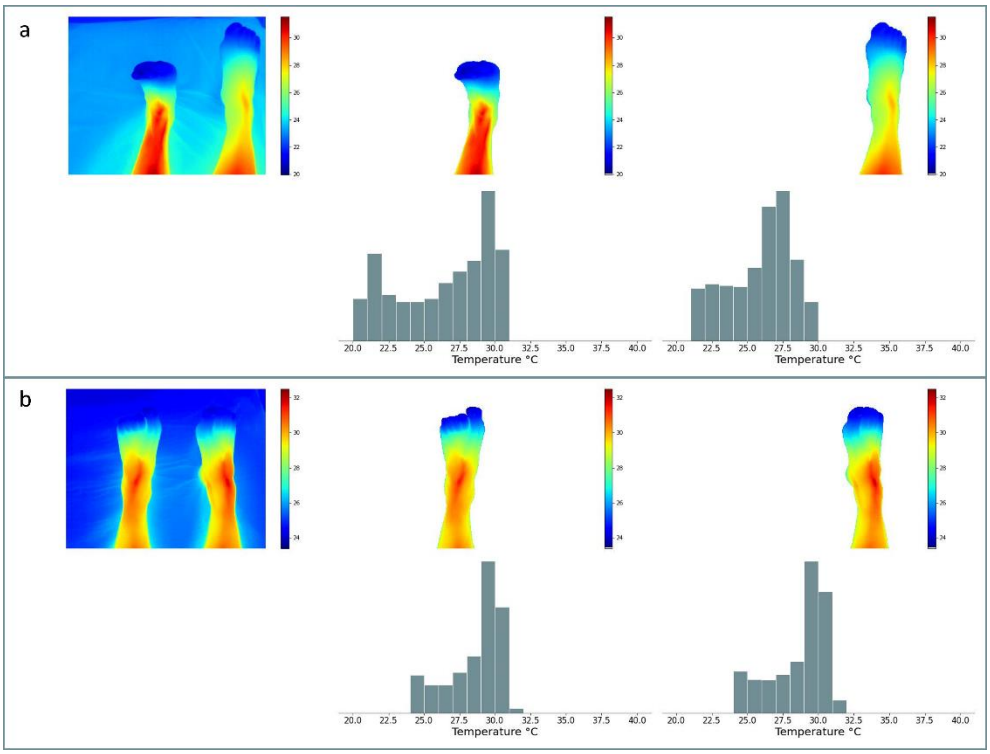


***Figure 9*** *The feet and ankles of patient 23*
*The right foot was affected, vasomotor symptoms were present at G0, and improvement at G1 was established by the physician and patient.*
*a. G0, with the right foot affected, which is visible on the foot's instep. However, the left foot has a different stance, creating less surface area.*
*b. G1, with improvement, the histograms of the thermographic images also show more similarities between left and right.*

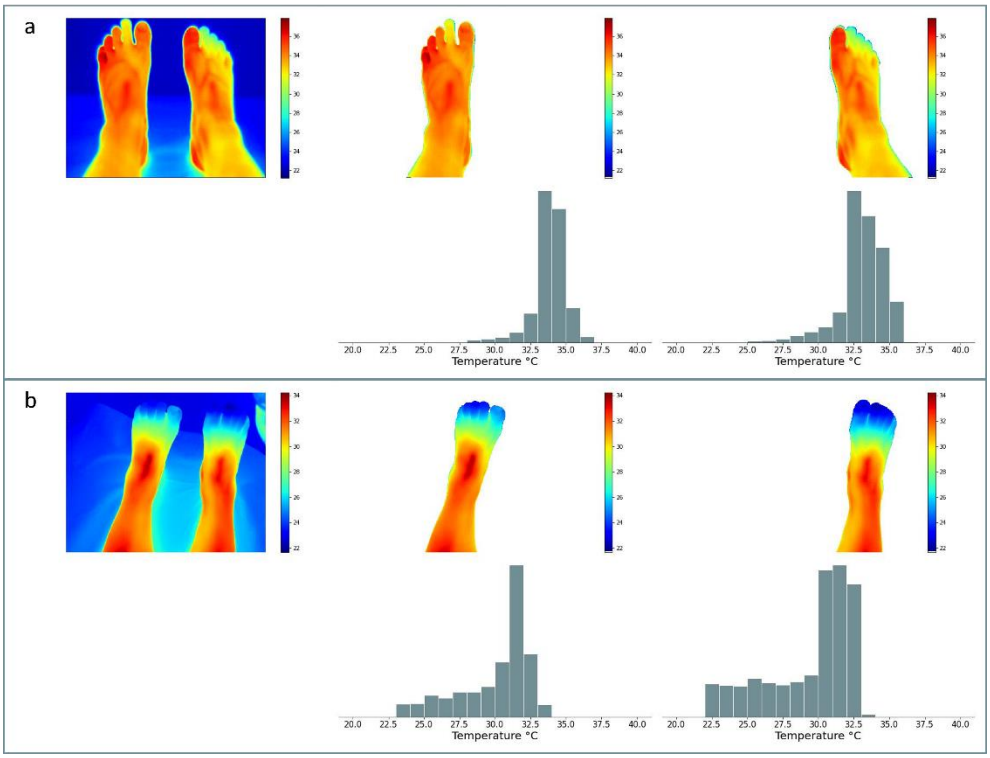


***Figure 10*** *The feet and ankles of patient 12*
*The right foot is affected; at G0, both feet were warm, and at G1, no distinction between left and right could be made, according to the physician and the patient.*
*a. G0, with the right foot affected*
*b. G1, without improvement; however, both feet are visually colder than at G0.*

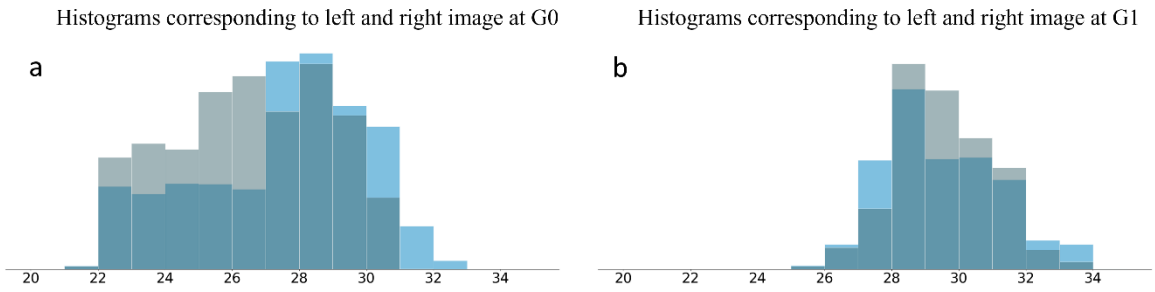


***Figure 11***. *Histograms of patient 13*
*Overlapping histogram of the left and right extremity at* ***a.*** *G0 and* ***b.*** *G1*

### 4.1.3 Reduction in histogram feature values after three months of SCS for all patients

**Figure 12** shows boxplots of the selected histogram features for all included patients. With 30 patients and 55 thermographic images on G0 and G1. When determine the difference between the two moments, two patients did not match, resulting in 28 patients and 50 thermographic images in **Figure 12b**. No statistically significant differences were found between G0 and G1: mean (p=0.607), median (p=0.312), minimum (p=0.877), maximum (p=0.552), peak (p=0.215), skewness (p=0.186), kurtosis (p= 0.415), quartile range (p=0.504). The boxplots in **Figure 12b** are around zero for each feature, indicating that there are patients with an increase and patients with a decrease between G0 and G1.

On average, the mean, median, peak, skewness, and quartile range show a negative mean and median difference between G0 and G1, indicating a decrease between G0 and G1 for all patients combined. This agrees with the hypothesis. While the other features are positive, representing an increase from G0 to G1.

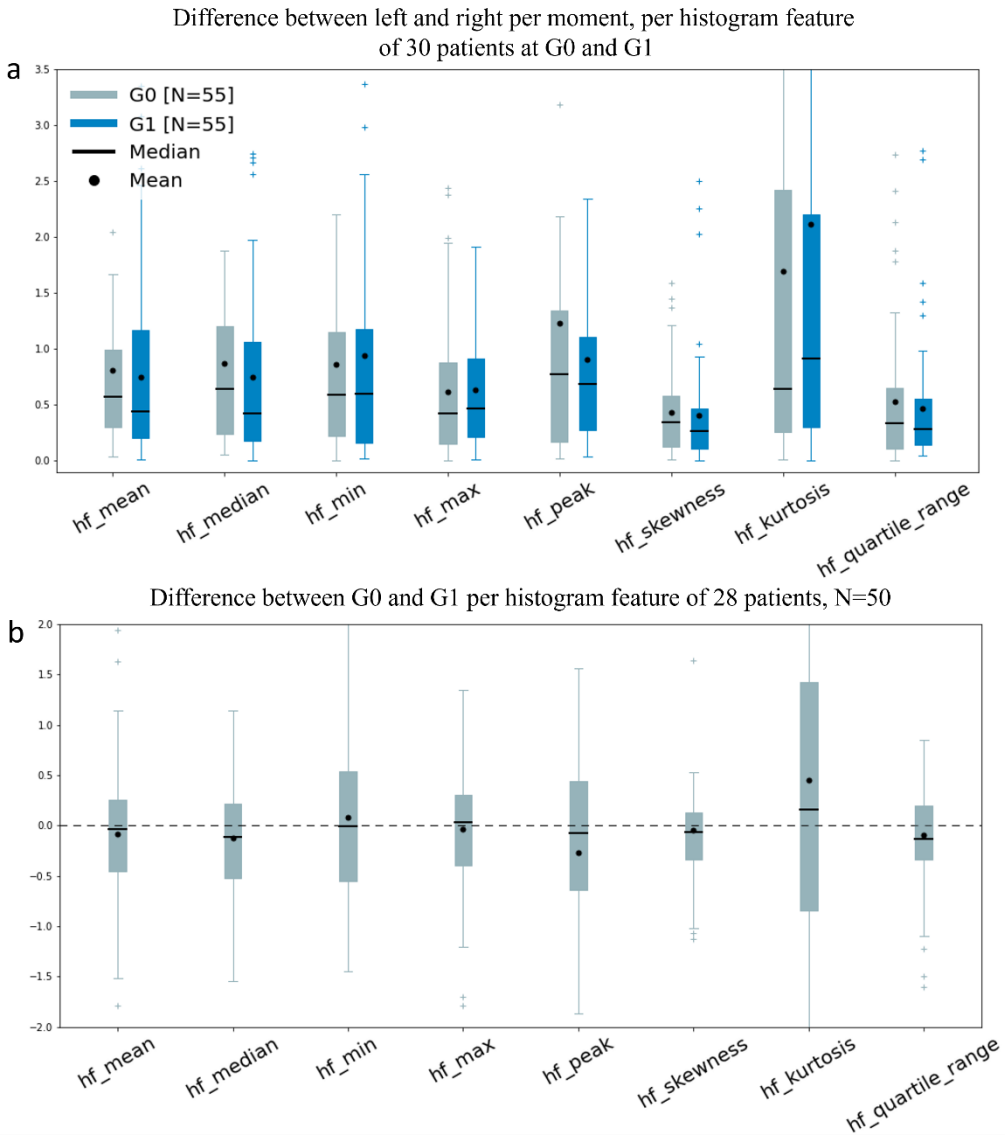


***Figure 12 a.*** *distribution per feature at G0 and G1 for all patients. 30 patients were included at both visits and 55 thermographic images were included. The absolute difference between left and right was calculated for each patient per moment. No significance was found between G0 and G1 for any feature.*
***b****. distribution per feature of difference between G1 and G0, calculated according to Equation 1 for 50 thermographic.*

### 4.1.4 Reduction after three months of SCS for patients with vasomotor improvement

#### 4.1.4.1 Vasomotor improvement for all patients

**Figure 13** shows the difference per feature between baseline and 3 months of SCS in boxplots for patients with and without vasomotor improvement.

According to the physician and the patients, 16 had improved symptoms, with 30 thermographic images (**Figure 13a**). The mean and median of the histogram feature values were slightly decreased for improved patients compared to not improved for the features mean, median, minimum, peak and quartile range. However, no statistically significant differences were found between improved and not improved for any feature: mean (p=0.120), median (p=0.247), minimum (p=0.851), maximum (p=0.263), peak (p=0.120), skewness (p=0.494), kurtosis (p=0.533), quartile range (p=0.130)

When the thermographic images were assessed visually for change in symptoms, 13 patients had improved vasomotor symptoms, with 22 thermographic images (**Figure 13b**). Again a general pattern of reduction was observed for a patient with improvement of vasomotor symptoms, agreeing with our hypothesis. In addition, the interquartile range of the mean, median, and quartile ranges were below zero and thus decreased for at least 75% of the images. Statistically significant differences are found with p-values < 0.05 in the following features: mean (p=0.003), median (p=0.004), maximum (p=0.007), peak (p=0.008), and quartile range (p=0.029). No statistically significant differences were found for: minimum (p=0.151), skewness (p=0.703), and kurtosis (p=0.488).

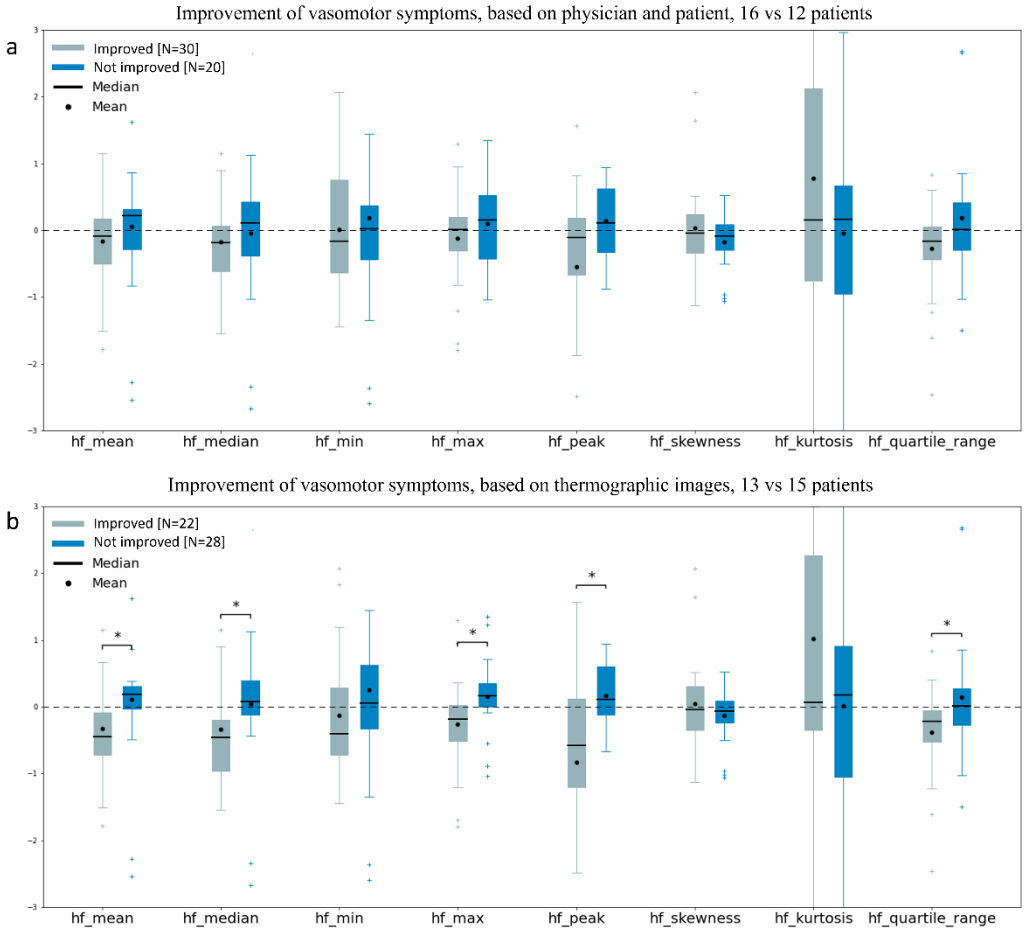


***Figure 13**. Distribution per feature of difference between G1 and G0 for thermographic images of patients with and without improvement of vasomotor symptoms.*
***a.** vasomotor improvement established by physician and patient with 30 images for improved patients and 20 for not improved. **b.** vasomotor improvement based on visual assessment of the thermographic images. With 22 images for improved patients and 28 for not improved. * statistically significant*

### 4.1.4.2 Vasomotor improvement for patients with vasomotor symptoms at baseline

**Figure 14a** shows the results in boxplots comparing patients with and without vasomotor symptoms at baseline. According to the physician, 20 patients with 36 thermographic images had vasomotor symptoms at baseline compared to 8 patients and 14 images without.

Patients with vasomotor symptoms showed a more decreased median and mean than those without vasomotor symptoms for features mean, median, minimum, peak, and quartile range. These features were also statistically different with p-value < 0.05: Mean (p=0.026), median (p=0.046), minimum (p=0.008), and quartile range (p=0.016). The other features were not statistically different: maximum (p=0.336), skewness (p=0.456), and kurtosis (p=0.991).

**Figure 14b** shows the results of the patients with vasomotor symptoms at baseline and how they discriminate with or without improvement. 14 patients with 25 thermographic images had an improvement and 6 patients without vasomotor improvement after 3 months of SCS, but the differences were not statistically significant. However, a decrease was seen in patients with improvement, which appears to be lower than in patients without improvement. This applies to the features mean, median, maximum, peak and quartile range. The p-values: mean (p=0.784), median (p=0.891), minimum (p=0.243), maximum (p=0.243), peak (p=0.243), skewness (p=0.810), kurtosis (p=0.706), quartile range (p=0.180).

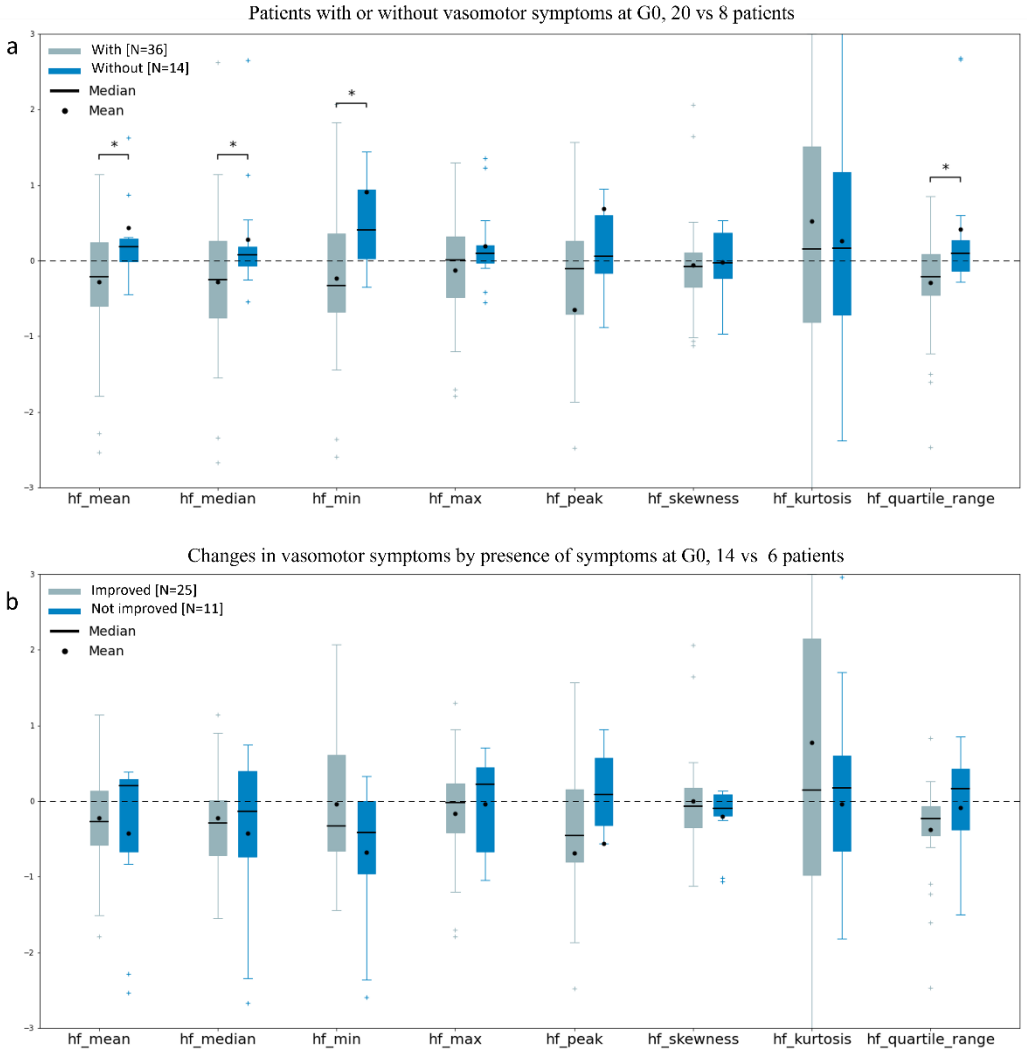


***Figure 14. a**. changes between G0 and G1 per histogram feature for thermographic images of patients with (N=36) and without (N=14) vasomotor symptoms at baseline. **b.** changes between G0 and G1 per histogram feature for improvement of vasomotor symptoms at G1 for patients 'with' vasomotor symptoms at baseline.*
** statistically significant*

#### 4.1.4.3 Vasomotor improvement depending on the affected extremity

There were only minor differences between the affected upper extremity, with 12 patients and 22 thermographic images, and the lower extremity, with 16 patients and 28 thermographic images, see *Appendix B*. No statistically significant differences were found between changes in histogram feature values from G0 to G1. Mean (p=0.353), median (p=0.618), minimum (p=0.429), maximum (p=0.732), peak (p=0.564), skewness (p=0.837), kurtosis (p=0.578), quartile range (p=0.914)

Of the patients with an affected upper extremity, 8 patients, with 14 images, had an improvement in symptoms versus 4 people, with 8 images, who did not have any improvement. There is no clear relation between patients who had improved symptoms and those who did not have improved. There appears to be a slight decrease in mean, median, peak, and quartile range attribute values for patients with improved vasomotor symptoms. Still, a moderate decrease was also found in median, max, skewness and kurtosis feature values for patients without improvement. Statistically significant differences with a $p < 0.05$ were only found for upper extremity skewness ($p = 0.029$), for which the improved patients had an increased difference between left and right at G1. No statistical differences were found in the other features: mean (p=0.714), median (p=0.973), minimum (p=0.714), maximum (p=0.973), peak (p=0.920), skewness (p=0.029), kurtosis (p=0.127), quartile range (p=0.525).

There appears to be a more reduced difference for the affected lower extremities for the 8 patients with 16 images, with the improvement than for the 8 patients without with 12 images. This is observed for the mean, median, minimum, maximum, peak kurtosis, and quartile range features, but only the peak was statistically significant (p=0.048). Mean (p=0.144), median (p=0.219), minimum (p=0.798), maximum (p=0.109), skewness (p=0.202), kurtosis (p=0.202), quartile range (p=0.236).

#### 4.1.4.4 Vasomotor improvement depending on CRPS type

The changes between G1 and G0 per histogram feature for patients with cold (16 patients), warm (3 patients), or a normal (9 patients) type of CRPS are shown in *Appendix B*.

In patients with cold CRPS, 11 patients with 19 thermographic images had improved vasomotor symptoms and showed a decrease in mean, median, minimum, maximum, peak, and quartile range features. Statistically significant differences between improved or no improvement were found with p-value < 0.05 for maximum (p=0.024), peak (p=0.016) and quartile range (p=0.027), of which the entire interquartile ranges of the data were below zero, and therefore it was assumed that the differences between the left and the right had decreased. The other feature values showed no statistically significant values: mean (p=0.105), median (p=0.140), minimum (p=1.000), skewness (p=0.555), and kurtosis (p=0.768).

Four patients were established with warm CPRS, and all patients had vasomotor improvement, according to the physician and patient. However, the boxplot distribution was mostly above zero, indicating an increased difference between the left and right sides.

In two patients with normal CPRS, there was an improvement in vasomotor disturbances. This could be explained by the fact that the physician saw no vasomotor symptoms at baseline, unlike the patient who did and also established improved symptoms at G1. In the 7 non-improving patients, the difference between G0 and G1 differs per feature. Because the improved group was too small, no statistically significant values were found.

## 4.2 Effect of closed-loop SCS on patients from the CL-study

The CL-study is ongoing and at the time of data analysis, four patients had at least a three-month follow-up visit. Of these patients, two completed the study and thus had a follow-up of up to 6 months, one had the 5-month visit to date, and the last had the 4-month visit. Because there are too few patients to compare, the results of the different measurements of the patients were assessed separately.

To determine the effect of SCS on the patient's vasomotor symptoms, the changes in histogram feature values of the thermographic images were first determined. For this purpose, the histogram features of the mean, median, minimum, maximum, peak and quartile range were used. The changes in the features were compared to the presence of vasomotor symptoms reported in the CSS, determined by the physician and patient.

Subsequently, the results of the CRPS severity score (CSS), Condition Pain Modulation (CPM), Temporal Summation (TS), blood samples and Fitbit data were analyzed to evaluate the effect of SCS on CNS dysregulation, inflammation, and activity, and to determine the effect of closed-loop versus open-loop per patient.

### 4.2.1 Patient CL04

This female patient was 22 years old at baseline and had CRPS in her left leg for three years. Her entire lower leg was affected and she had an NRS score ranging from 5 to 8 at baseline. In addition, she had symptoms such as hyperalgesia, vasomotor symptoms with a colder and blue-colored skin, foot swelling, edema formation, and sudomotor symptoms. As well as, dystrophic changes of the nails, and motor abnormalities with reduced strength and range of motion. For the randomization, she got closed-loop between 3 and 4 months and open-loop between 4 and 5 months. During the 5-month visit, she indicated that she preferred the closed-loop settings, which had been set up in the last month until the end of the study.

#### 4.2.1.1 Changes in vasomotor disturbances

At 3 months, physical examination showed partial improvement in vasomotor symptoms, mainly with more similar temperature to the unaffected side, which was also the case at the follow-up moments. **Figure 15** shows the of histogram feature values of thermographic images taken at baseline and the follow-up visits with SCS treatment. The figure shows that from baseline to 3 months SCS, all features, except the minimum, show an increase in the difference between the left and right sides. This increase does not correspond to the hypothesis. However, a decrease can be seen at the follow-up moments compared to 3 months of SCS. At 4 months, this is also below baseline, but for 5 and 6 months, this differs little from the baseline measurement and is therefore also inconsistent with the hypothesis.

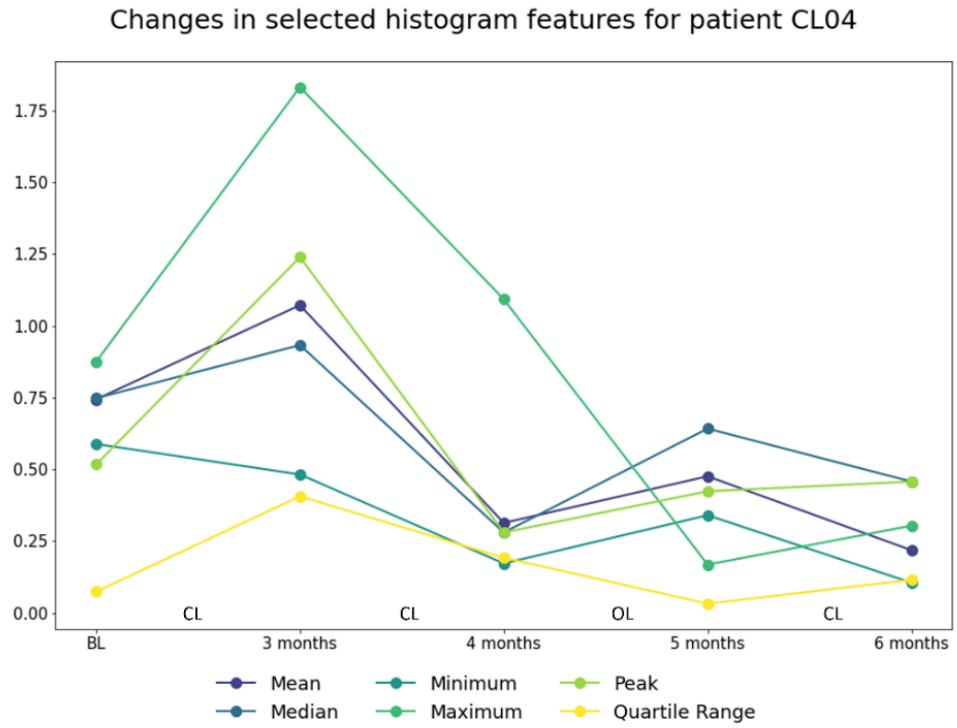


***Figure 15**. Calculated histogram features based on thermographic images of patient CL04. The absolute difference between the left and right extremities is determined at measurement moments: baseline (BL), 3, 4, 5, and 6 months for each selected histogram feature. CL = closed-loop, OL = open-loop*

#### 4.2.1.2 Changes in CRPS severity score

**Table 1** shows the CSS results, which decrease after 3 months of SCS and remain low. Documentation of the anamnesis and physical examination shows that in addition to pain reduction, most symptoms have improved, such as hyperalgesia, temperature asymmetry, and edema, after 3 months of SCS. Although the red color, some dystrophic differences and weakness continued to improve partially but not completely.

#### 4.2.1.3 Changes in CNS dysregulation

For the effect of SCS on CNS dysregulation, the results in the table show a reduction in pain based on the NRS scores. With CPM, you see a decrease at 3, 4 and 6 months, where a closed loop has been set. This is to be expected with an improvement of the inhibitory pathway. At 5 months, the CPM is incremented with the open-loop setting. The TS was 0 at follow-up measurements, as the patient reported an overall NRS score of 0.

#### 4.2.1.4 Changes in inflammation and activity

In terms of inflammation, the patient was always below the maximum value of 555 U/ml, which did not change after SCS therapy. Looking at activation, the table shows an average increase of approximately 1000 steps at 3 months of SCS compared to baseline, with a continuously increasing number of steps at follow-up visits.

***Table 1.*** *Results from various measurements of patient CL04.*

| | BL | 3 months | 4 months | 5 months* | 6 months |
|---|---|---|---|---|---|
| NRS | 5 | 0 | 0 | 0 | 0 |
| NRS 24 H | 8 | 0 | 0 | 0 | 0 |
| CSS | 14 | 6 | 5 | 7 | 5 |
| CPM | 0.15 | -0.08 | -0.03 | 0.74 | 0.07 |
| TS | 0.4 | 0 | 0 | 0 | 0 |
| sIL-2R | 322 | 283 | 301 | 310 | 318 |
| steps | 1012 | 2000 | 2387 | 2471 | 3901 |

*Results of the measurements, determined at moments: baseline (BL), 3, 4, 5 and 6 months. NRS = Numeric rating scale, the pain score at that moment. NRS 24 H = the pain score of the previous 24 hours. CSS = CRPS severity score. CPM = Conditioned Pain Modulation. TS = Temporal Summation. sIL-2R = soluble IL – 2 receptor. * open-loop setting*

#### 4.2.1.5 Closed-loop versus open-loop

The patient ultimately chose the closed-loop setting after the randomization process. In addition, a difference between closed-loop and open-loop is visible in the CSS score of 2 points, which is higher at 5 months than at 4 and 6 months. An increased CPM is also visible at 5 months. The histogram features show an increase in mean median, minimum, and peak, while the others decrease at 5 months. No specific differences were observed in the other tests.

#### 4.2.1.6 Comparison of measurement results

The patient is ultimately very satisfied with the stimulation and improved on all CRPS mechanisms. Vasomotor symptoms are improved based on the CSS, while the calculated histogram feature values are reduced only at 4 months. The improvement in symptoms of both vasomotor disturbances and central nervous system dysregulation is simultaneous. Comparing closed-loop and open-loop shows a diminished effect on CNS dysregulation and motor function symptoms based on CSS, and CPM is evidently increased during open-loop. In contrast, vasomotor symptoms remain the same according to the CSS results, and histogram features increase only slightly between 4 and 5 months.

### 4.2.2 Patient CL05

This female patient was 47 years old and had CRPS in her right foot for over two years at baseline. The location is primarily the lateral side of her foot and ankle, with an NRS score of 8. She reported CNS symptoms consisting of allodynia and hyperalgesia, as well as vasomotor symptoms with a blue and colder foot. Furthermore, there was sweat asymmetry, edema, and dystrophic skin changes, and she had motor abnormalities resulting from a foot drop. With the randomization, she first got an open-loop between 3 and 4 months and a closed-loop between 4 and 5 months. In the end, she preferred the closed-loop settings, which were set until the end of the study.

#### 4.2.2.1 Changes in vasomotor disturbances

After three months with SCS, physical examination showed partial improvement in vasomotor symptoms, mainly with more symmetrical skin temperature and color. While at follow-up moments, the skin of the affected side was slightly colder. **Figure 16** shows the change in histogram features of thermographic images taken at baseline, and the follow-up visits 6 months with SCS. The figure shows that from baseline to 3 months, all feature values indicate a decrease in the difference between left and right, which is in line with the expected reduction, except for the minimal feature. Subsequently, there is a slight increase for the mean, median, and maximum at follow-up visits, which corresponds to the findings of the CSS. But the values are still below the baseline values. The quartile range and minimum features have a slightly different course.

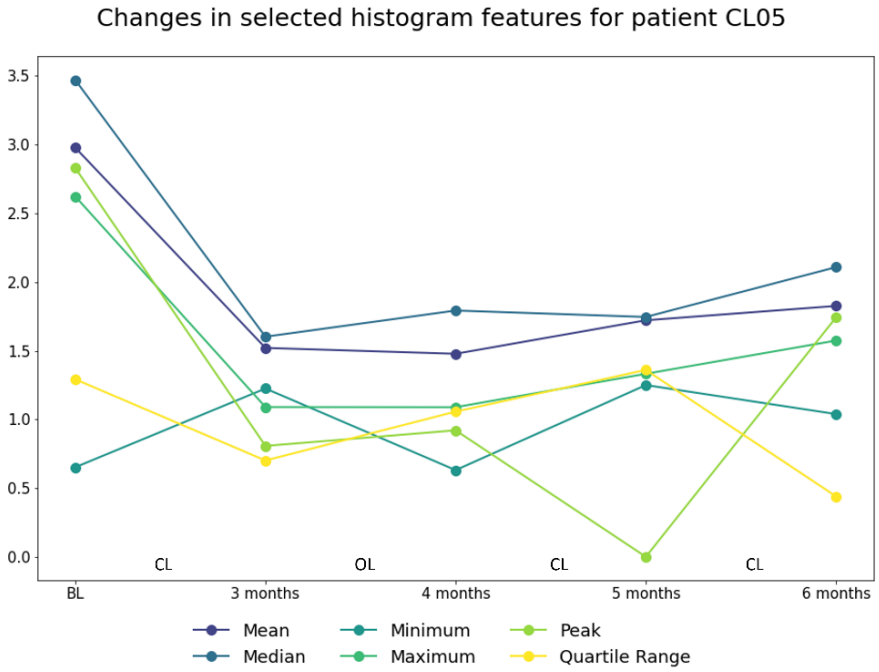


***Figure 16.*** *Calculated histogram features based on thermographic images of patient CL05. The absolute difference between the left and right extremities is determined at measurement moments: baseline (BL), 3, 4, 5, and 6 months for each selected histogram feature. CL = closed-loop, OL= open-loop*

#### 4.2.2.2 Changes in CRPS severity score

The CSS results shown in **Table 2**, slightly decreased after 3 months CSC, and remained increased in the follow-up visits. Documentation of the CSS showed an improvement in vasomotor symptoms, sweating and dystrophic changes, while CNS symptoms were still present.

#### 4.2.2.3 Changes in CNS dysregulation

For the effect of SCS on CNS dysregulation, the table shows a decrease in NRS scores at three months, which increases at the follow-up visits. After 3 months of SCS, the CPM results are reduced, while at 4 to 6 months, the CPM rises, which corresponds with the CSS results. The TS was only elevated at 4 months, but the reported NRS scores were here elevated for the unaffected side as well, making the scores more similar to the affected side and thus the TS results less reliable.

#### 4.2.2.4 Changes in inflammation and activity

In terms of inflammation, the patient was already below the maximum value of 555 U/ml at baseline, and this value decreased slightly after SCS therapy. Looking at activation, the table shows an increase of about an average of 2000 steps from 3 months of SCS compared to baseline, these increases remained about the same at follow-up visits.

#### 4.2.2.5 Closed-loop versus open-loop

The patient ultimately chose the closed-loop setting after the randomization path. In addition, a difference between closed-loop and open-loop is visible in the NRS score, with open-loop having an NRS score of 7 compared to a closed-loop NRS score of 4 and 6, but other symptoms showed no real difference. The CPM was higher with the closed-loop at 5 and 6 months, but not at 3 months, while the TS was regarded as unreliable. The histogram features remain the same, except that the quartile range decreases and the activity increased with closed-loop.

***Table 2*** *Results from various measurements of patient CL05*

| | BL | 3 months | 4 months* | 5 months | 6 months |
|---|---|---|---|---|---|
| NRS | 8 | 2 | 7 | 4 | 6 |
| NRS 24 H | 8 | 2 | 6 | 6 | 9 |
| CSS | 15 | 10 | 10 | 11 | 12 |
| CPM | 0.26 | -0.10 | 0.38 | 0.59 | 0.64 |
| TS | 0.45 | 0.44 | -0.02 | 0.20 | 0.97 |
| sIL-2R | 344 | 307 | 238 | 256 | 274 |
| steps | 4696 | 668 | 6132 | 7280 | 6540 |

*Results of the measurements, determined at moments: baseline (BL), 3, 4, 5 and 6 months. NRS = Numeric rating scale, the pain score at that moment. NRS 24 H = the pain score of the previous 24 hours. CSS = CRPS severity score. CPM = Conditioned Pain Modulation. TS = Temporal Summation. sIL-2R = soluble IL – 2 receptor. * open-loop setting*

#### 4.2.2.6 Comparison of measurement results

After 3 months of SCS, patient CL05 showed improvement in NRS score, CPM, step count, and vasomotor symptoms based on both thermogram features and CSS results. With the open-loop setting between 4 months, the NRs score increases compared to 3 and 5 months. As well as the CPM result at 4 months compared to 3 months, the CPM score at 5 and 6 months increased, while the step counts improved at all times after SCS therapy, indicating an improvement in activity. The NRS score and other symptoms worsen towards the end of the study. Therefore, the patient is eligible for revision to improve the stimulation area.

### 4.2.3 Patient CL06

Patient CL06 was a 32-year-old female with CPRS in her left leg for four years, with dystonia of her ankle, and the pain primarily in her foot at baseline. She reported an NRS score of 6-8 associated with allodynia, hyperalgesia, vasomotor symptoms with a cold purple foot, sudomotor symptoms, dysmorphic changes, and motor abnormalities. The patient is still in the study and was evaluated from baseline to her 5-month visit. With the randomization, she first received a closed-loop between 3 and 4 months and an open-loop between 4 and 5 months. However, she had a sympathetic block with botox two weeks before the 4th month visit. This may have affected the results at 4 and 5 months. In the end, she preferred the closed-loop settings, which were set for the last month of the study.

#### 4.2.3.1 Changes in vasomotor disturbances

After three months of SCS, vasomotor symptoms were still present, with cold and blue skin assessed by physical examination, reported on the CSS document. There was a slight color improvement in the follow-up moments, while the foot remained cold. **Figure 17** shows the change in the histogram features from baseline to 5 months follow-up. After 3 months, apart from a reduction in the quartile range, there were only minimal changes in the other features. While between 3 and 4 months, there is a decrease in all features, which increased again between 4 and 5 months when the patient had open-loop SCS.

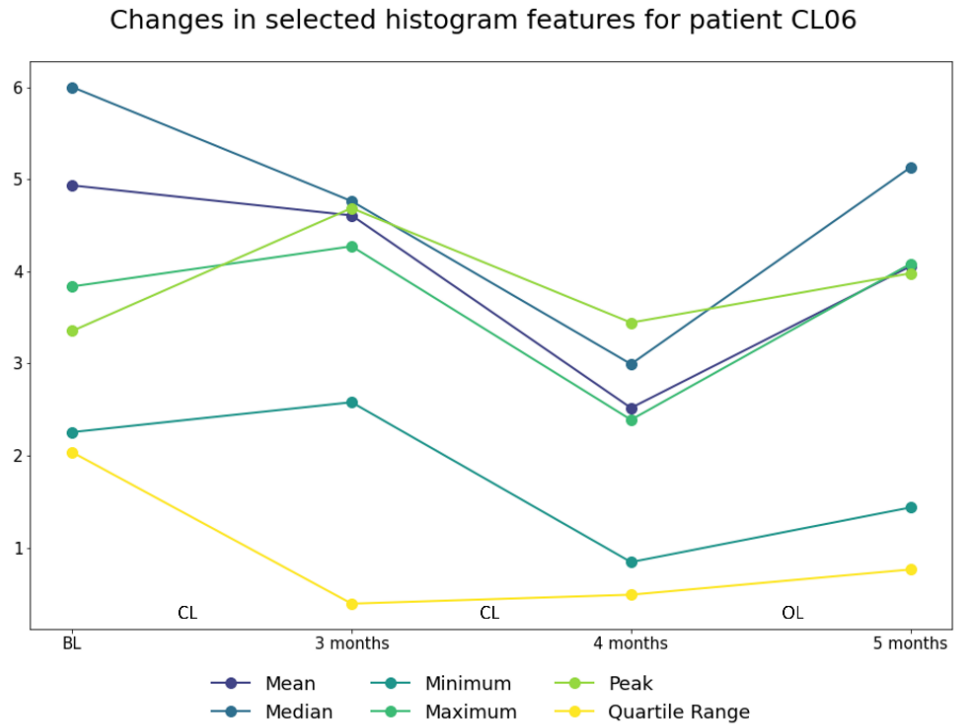


***Figure 17.*** *Calculated histogram features based on thermographic images of patient CL06. The absolute difference between the left and right extremities is determined at measurement moments: baseline (BL), 3, 4, and 5 months for each selected histogram feature.*

#### 4.2.3.2 Changes in CRPS severity score

The CSS results in **Table 3** remained approximately the same for all visits, and only the symptoms of color, sweating and edema improved over time.

#### 4.2.3.3 Changes in CNS dysregulation

For the effect of SCS on CNS dysregulation, the table shows no actual reduction in NRS scores after SCS. With CPM, an increase is seen at three months, while a decrease from baseline is seen at months 4 and 5. The latter corresponds to an improved inhibition pathway. The TS was not applied after 3 months of SCS because the patient found it too painful.

#### 4.2.3.4 Changes in inflammation and activity

In terms of inflammation, the patient was already below the maximum value of 555 U/ml at baseline, which remained the same after SCS therapy. Looking at activation, the table shows no increase in the number of steps, even a slight decrease of about 1000 steps between 4 and 5 months.

#### 4.2.3.5 Closed-loop versus open-loop

The patient ultimately chose the closed-loop setting after randomization. In addition, a difference between closed-loop and open-loop is visible in the higher CPM and the lower number of steps between 4 and 5 months. The histogram features also show an increase between 4 and 5 months, returning them to baseline values.

***Table 3**. Results from various measurements of patient CL06*

| | BL | 3 months | 4 months | 5 months* |
|---|---|---|---|---|
| NRS | 8 | 7 | 7 | 7.5 |
| NRS 24 H | 6.5 | 8 | 8 | 8.5 |
| CSS | 13 | 12 | 13 | 14 |
| CPM | 0.10 | 0.43 | -0.13 | 0.03 |
| TS | -1.13 | Nan** | Nan** | Nan** |
| sIL-2R | 268 | 378 | 323 | 342 |
| steps | 5874 | 6314 | 5198 | 4612 |

*Results of the measurements, determined at moments: baseline (BL), 3, 4 and 5 months. NRS = Numeric rating scale, the pain score at that moment. NRS 24 H = the pain score of the previous 24 hours. CSS = CRPS severity score. CPM = Conditioned Pain Modulation. TS = Temporal Summation. sIL-2R = soluble IL – 2 receptor. * open-loop setting ** stopped TS*

#### 4.2.3.6 Comparison of measurement results

At the end of the study, the patient was not satisfied with the stimulation and still had high NRS scores. Therefore, this patient is also being considered for revision to a different type of SCS. Regarding vasomotor symptoms, improvement in patient CL06 is only visible after 4 and 5 months. This shows an improvement in the CSS and a reduction in the histogram features. This is consistent with improving CNS dysregulation due to decreasing CPM and a slight decline in NRS. In addition, this patient also shows that closed-loop gives slightly better vasomotor and CNS results, both with improvement with the CSS, the thermograms, and the CPM. However these results could be affected by the botox treatment. During the follow-up visits, the patient still had many complaints, and the NRS score did not decrease much, while the NRS daily score even increased compared to baseline.

### 4.2.4 Patient CL07

Patient CL07 was a 31-year-old female with CRPS of her right lower leg for 20 years at baseline. The primary painful area was from the lateral side of the ankle to her front foot, with a corresponding NRS of 8. In addition, she had allodynia, hyperalgesia, and a slightly colder, blue-colored foot compared to the healthy side, as well as edema and dystrophic changes in her nails and hair growth. Her foot was weak, and she often had dystonia of her ankle. The patient is still in the study and was evaluated from baseline to her 4-month visit. With the randomization, she first got an open-loop between 3 and 4 months and a closed-loop between 4 and 5 months. However, the 5-month measurement has not yet taken place, so the desired effect is unknown.

#### 4.2.4.1 Changes in vasomotor disturbances

At baseline, the patient reported a cold and blue right foot as vasomotor symptoms, while the physician noted no temperature asymmetry. After 3 months, there is an improvement in vasomotor symptoms, with no color differences, and the patient only reports a colder foot. After 4 months, both physician and patient indicated that the foot was a bit colder and with a color difference.

**Figure 18** shows the histogram of the thermographic images from baseline to 4 months of SCS stimulation. Most features decrease between baseline and 3 months SCS but increase again between 3 and 4 months SCS, corresponding with the CSS results. Only the minimum and quartile ranges had a different course, with the quartile range further decreasing and the minimum feature increasing.

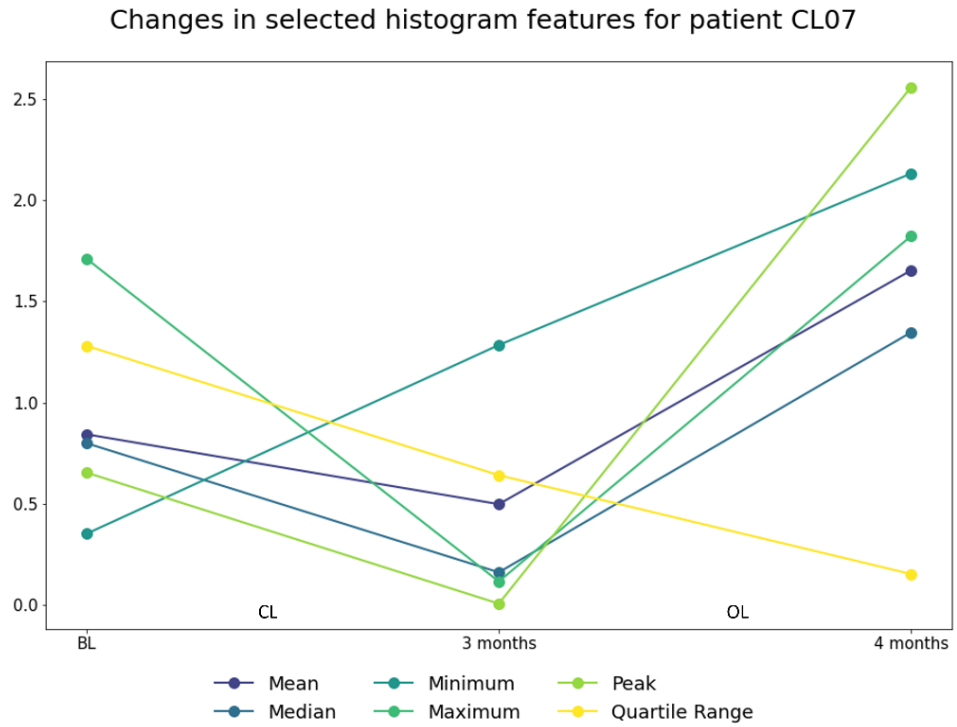


***Figure 18.*** *Calculated histogram features based on thermographic images of patient CL07. The absolute difference between the left and right extremities is determined at measurement moments: baseline (BL), 3 and 4 months for each selected histogram feature.*

#### 4.2.4.2 Changes in CRPS severity score

CSS results in **Table 4** decreased 2 points and documentation stated that symptoms of CNS dysregulation persisted, both allodynia and hyperalgesia. However, at 3 months, the symptoms had decreased slightly compared to baseline and 4 months. But mainly the vasomotor, sudomotor and dystrophic symptoms decreased at 3 months.

#### 4.2.4.3 Changes in CNS dysregulation

For the effect of SCS on CNS dysregulation, the result shows no actual reduction in NRS scores after SCS, going from an 8 to a 7. Also, CPM has almost no differences between the three moments. At the same time, TS measurement was stopped at baseline and after 3 months because it was perceived as too painful, while after 4 months, both the single and repeated pain stimulus NRS scores were so high that they were indistinguishable.

#### 4.2.4.4 Changes in inflammation and activity

In terms of inflammation, the patient was already below the maximum value of 555 U/ml at baseline, which remained the same after SCS therapy. Looking at activation, the table shows a slight increase in the number of steps after 3 months, which is equal to the baseline at 4 months. Furthermore, the patient walks with crutches and continues to do so after 4 months of SCS.

***Table 4*** *Results from various measurements of patient CL07*

| | BL | 3 months | 4 months* |
|---|---|---|---|
| NRS | 8 | 7 | 7 |
| NRS 24 H | 8 | 7 | 8 |
| CSS | 12 | 10 | 10 |
| CPM | -0.02 | 0.04 | -0.02 |
| TS | 1.29** | Nan** | 0.28 |
| sIL-2R | 462 | 386 | 416 |
| steps | 1875 | 2453 | 1811 |

*Results of the measurements, determined at moments: baseline (BL), 3, 4 and 5 months. NRS = Numeric rating scale, the pain score at that moment. NRS 24 H = the pain score of the previous 24 hours. CSS = CRPS severity score. CPM = Conditioned Pain Modulation. TS = Temporal Summation. sIL-2R = soluble IL – 2 receptor. * open-loop setting ** stopped TS*

#### 4.2.4.5 Comparison of measurement results

In this patient, there is a slight improvement in vasomotor and CNS symptoms. However, this is only reflected in the two-point reduction in CSS and reduction in features in the thermograms after 3 months of SCS. The patient had only slightly improved CPRS symptoms in the trial period and after permanent implantation, but this was enough for her to have a better quality of life.

# 5 Discussion

The results of quantifying the thermographic images based on the FR-study data are discussed in section 5.1, followed by the measurement results performed on the patients in the CL-study in 5.2. A conclusion for both studies is drawn in 5.3.

## 5.1 Thermographic images FR-study

Changes in several histogram feature were examined to quantify the effect of SCS on vasomotor improvement in CPRS patients. I assumed that effective treatment of SCS in vasomotor symptoms would reduce the differences between left and right histogram feature values. The results showed a few statistical differences between patients with and without improvement of vasomotor symptoms, with a slight decrease in the mean, median, peak, and quartile range features.

### 5.1.1 Interpretation of thermographic images and histograms

Different histogram features were selected after visual interpretation of the thermographic images; mean, median, minimum, maximum, peak, skewness, kurtosis and quartile range. The selection was based on different properties of the histograms, where the distribution, density and peaks on the affected side were distributed differently than on the unaffected side.

The distribution difference between the affected and unaffected sides is more evident in patients with cold CRPS. There seems to be less difference in patients with warm CRPS. This could be explained by the fact that warmer distal extremities are not so different from the temperature proximal in the body. In contrast, distal parts that get cold will deviate more from proximal temperatures.

### 5.1.2 Reduction in histogram feature values after three months of SCS for all patients

When all patients were taken together, no statistical relationship was shown in the decreased histogram feature values between G0 and G1. The features median, peak and quartile range showed a slight reduction between G0 and G1, indicating a more similar distribution between left and right. However, the changes were small, and there were no significant differences between G0 and G1. Logical because no distinction was made between patients. Thus, patients who showed no improvement and initially had no or hardly any vasomotor complaints at G0 were added.

### 5.1.3 Reduction in histogram feature values for patients with vasomotor improvement

Patients with vasomotor improvement, established by the physician and patient, showed a slight decrease in most histogram feature values after three months of SCS. This supports the hypothesis that, with an improvement in vasomotor symptoms, the difference between affected and unaffected extremities is reduced after SCS. However, the reductions were minor, and outliers showed that not all patients had a decrease when improved. Moreover, some patients without improvement also showed decreased feature values after SCS.

In patients whose vasomotor improvement was assessed visually on the thermographic images, some statistical difference could be observed compared to patients without improvement. However, these changes in feature values are reasonably expected because the shift in vasomotor symptoms observed in the images is more likely to match the histograms and, thus the calculated features.

Between the vasomotor improvement observed by physician and patient and assessed visually on the thermographic images, seven patients did not match. These patients showed minimal improvement. For example, a patient who had no improvement, according to the physician and the patient had a less cold foot after three months, but the physician still determined that it was cold, while the images show a slight improvement. The physician mainly looked at the presence of any symptoms and therefore looks binary, while images can be used to look at any change. In contrast, with thermographic images, an improvement in the fingertip will be less noticeable when the whole hand is photographed, while the physician can determine improvement. Furthermore, the assessment of the thermographic images is done by me rather than the physician, so these results may not be compatible.

For patients with vasomotor symptoms at baseline, established by the physician, no statistical differences were found between improved and not improved vasomotor symptoms. However, according to the patients themselves, only two had no vasomotor symptoms at baseline. Therefore, the changes in histogram feature values between G0 and G1 would be more comparable to the changes in all patients with improved symptoms, shown in *4.1.4.1*. Determining vasomotor symptoms at baseline requires more data from patients with and without symptoms.

Comparing the extremities, the trend of reduction between G0 and G1 with improvement was observed in more features for the lower extremities, showing a less consistent relationship between patients who did or did not improve for the upper extremities. The difference between the upper and lower extremities may be principally due to the size differences. However, it is also possible that hands are often warmer than feet. As described, this corresponds with different distributed histograms, which could affect the selected features differently. More data is needed to conclude with more certainty.

In patients with cold CRPS, the expected reduction is observed in histogram features after 3 months of SCS with even the entire interquartile range beneath zero for the mean, median and quartile range. However, there are only some patients with warm and normal CPRS types in this dataset. Patients with warm and normal CPRS have no decrease or even an increased difference between left and right after 3 months of SCS. Better differentiation between the type of CRPS is an addition to distinguishing vasomotor improvements further.

### 5.1.4 Selected histogram features

Of the selected histogram features, the mean, median, minimum, maximum, peak and quartile range appear to have the expected reduction after three months of SCS. These features were, therefore, also investigated in the patients of the CL-study. Skewness and kurtosis often deviate from the expected decrease. Both functions look at the tail of the histogram, taking into account the direction, density, or the number of peaks but not the range of the values. The different change of skewness and kurtosis may be due to the calculation of the absolute difference between the left and right extremities. Since skewness and kurtosis can have a positive or negative value depending on the direction of the tail, this is eliminated by the absolute difference.

### 5.1.5 Limitations

The results presented here are from all thermographic images with affected limbs of patients at G0 and G1. As a result, the same number of images was not added for each patient. For example, one patient may have only one image taken, while another may have three. This was done to access more data to determine the results. However, because the number of images per patient is not taken into account, the results of some patients are given more weight, which can influence the results.

It was chosen to calculate the difference between the left and right extremities, with the unaffected side considered healthy. But in CRPS patients, this may not be entirely the case. As a result, possible changes between left and right that now attributed as improvements could be misinterpreted.

There was a difference between the physician's and the patient's interpretation of vasomotor symptoms at baseline. 29 patients reported vasomotor symptoms, while the physician only reported 22 patients with vasomotor symptoms at baseline. This could be explained as the measurement is only a snapshot for the physician, therefore might not always correspond to the presence of vasomotor disturbances. Furthermore, the vasomotor improvement after 3 months of SCS was based on both patient's and physician's assessment of color and temperature changes. In contrast, the symptoms at baseline were only defined by the physician. Thus, the presence of symptoms should be defined more consistently to compare baseline vasomotor symptoms with improvement of these symptoms after SCS.

The physician confirmed 4 patients with warm CPRS, but visually more patients had slightly warmer extremity temperatures on the thermographic images. These patients, who had warm temperatures in the images, are now not distinguished from patients with cold temperatures. This could have a different effect on the changes in the histogram feature values, as the patients with warm CPRS all had an increase in the differences in feature values. This increase in value differences between left and right after SCS may be related to less spread of the histograms, with a more limited range due to the higher temperatures. Yet, this could also be a coincidence since only few patients had warm CRPS.

Because this was an exploratory study, we did not perform a power calculation and correction for multiple comparisons beforehand. Since the groups got smaller with each question, the power is probably low and statistical differences cannot be considered significant with certainty. Therefore, it is recommended to look at more patients for this analysis in order to apply a power calculation and a multiple comparison correction.

### 5.1.6 Recommendations

Because using the absolute difference can lead to information being lost, it can be helpful to determine the difference between the affected and the healthy side. Due to external influences, such as weather or activity, patients may have a different temperature distribution between measurement times, so changes in the affected extremity alone should not be assessed based only on the temperature. However, the difference between affected and unaffected extremities could be calculated per moment. To achieve this, a clear distinction should be made about which side is affected at measurement moment. Using the difference may allow better analysis of the effects of other features, such as skewness and kurtosis.

The expected reduction can be seen in several patients combined for some features, but the tables from *Appendix C* show that in patients with vasomotor improvement, not always the same histogram features show a reduction in the absolute difference between left and right. A solution could be to combine the histogram functions using a machine-learning model. Because the histogram features look at different properties of the temperature distribution, a better distinction could be made between various properties of CRPS if a combination of histogram features is used. For example, by using the quartile range in conjunction with skewness or kurtosis, the tail properties of the histogram can be correlated with the temperature range, potentially allowing warm and cold CPRS phenotypes to be distinguished. As described, this has been applied by Bijl et al. (34). They discovered that the histogram features are already sufficient to distinguish between the presence or absence of CPRS in patients. With more information, changes in vasomotor symptoms could also be identified.

In addition, it may be necessary to assess the vasomotor symptoms of CRPS patients, more specifically, to determine any improvement in vasomotor symptoms. For this, several physicians could assess the symptoms using a physical examination and thermographic images and their findings should be compared. With this data, a model can be trained to determine vasomotor improvement.

## 5.2 Effect of closed-loop SCS on patients from the CL-study

In the four patients evaluated, an effect of SCS has been seen on both vasomotor disturbances and CNS dysregulation. This effect is mainly visible in the CSS results, but CPM results and histogram features of the thermographic images also show changes, which corresponds to improvements in the mechanisms. The patients had no inflammatory values to begin with.

The three patients who had completed the randomization opted for the closed-loop SCS. In addition, there was a difference with the open-loop setting, where the value of NRS and CSS increased compared to the closed-loop for patients CL05 and CL06.

### 5.2.1 Study population

The patients all had a positive trial two weeks before permanent implantation. However, SCS only had the desired effect in a few patients. For example, patients CL05 and CL06 are being considered for revision. The lack of the desired effect may be because permanent implantation would occur when minimal improvement was observed during the trial, as patients often regarded SCS as a last resort. But patient CL07, for example, was already satisfied with the small improvement in her symptoms.

At baseline, they all showed vasomotor disturbances and CNS dysregulation symptoms. Inflammation was not found, as the sIL-2R levels were normal. It appears that SCS had a different effect on the mechanism between patients. This may be because all patients had a slightly different phenotype of CRPS.

### 5.2.2 Thermographic images

From the thermographic images from the FR study, the mean, median, minimum, maximum, peak, and quartile range features were analyzed per patient. Between patients, you see a more or less comparable decrease in histogram features compared to an improvement in vasomotor symptoms, according to the CSS. However, this is not consistent for the same features per patient, which corresponds to the tables in *Appendix C*. Furthermore, the patients have a varying range on the y-axis corresponding to the difference between left and right per feature. Therefore, it is better to use a model to combine the features to get a more accurate result about the possible improvement of vasomotor symptoms.

In addition, thermographic images are an indirect indication of microcirculation. They are a single point in time, where, as in CPRS, the patient's temperature changes can be dynamic or change due to ambient temperature (19). Furthermore, the images cannot distinguish whether the improvement in vasomotor symptoms is due to an improvement in endothelial dysfunction or ANS dysregulation.

### 5.2.3 CPM and TS

The CPM results differ per patient and do not conclusively indicate an improvement in pain processing in SCS. This is consistent with the results of Kriek et al. (2022), who found little effect after 3 months of SCS on CPM results (39). The TS findings were incomplete, as the test was often excruciating in CRPS patients because of hyperalgesia of their affected extremities. Therefore the test could usually not be adequately performed.

SCS probably directly affects CNS dysregulation, but this is only objectively measured through CPM and TS and subjectively through CSS and NRS. However, CPM and TS also use the NRS score per measure. As a result, these tests are also partly subjective, and the environment can influence the outcome. For example, CPM can be affected by anxiety or the presence of other people. The tests were also not always performed by the same physicians, and thus the patients may have responded differently. This can affect the results of both the CPM and the TS.

In addition, the CPM test was repeated after the ice water. However, this pain stimulus had sometimes already worn off with the second round. Furthermore, the patient did not always experience

the stimulation as painful but sometimes as annoying, which can also influence the results between measurement moments.

### 5.2.4 Inflammation

Since all four patients did not have elevated sIL-2R levels, which would indicate the presence of inflammation, it is impossible to determine the effect of SCS on inflammation in these patients. Inflammation may not be present, as patients eligible for SCS are more likely to have long-standing CRPS and are often in the chronic phase, where inflammation is often less prominent.

### 5.2.5 Activity

The patients often showed some improvement in step count when other symptoms and pain scores improved. This indicates that when CRPS improves, the patient is more active, while the mobility of the extremities could also be improved. To measure the activity of the patients, Fitbit is used to count their footsteps. However, these measurements were not always accurate. For example, the movements of a wheelchair are also included in the number of steps.

### 5.2.6 Recommendations

It is still an ongoing study, and to learn more about the effect of SCS on the mechanisms, more patients need to be added to the study.

In addition, the immediate effect of SCS can also be evaluated using data measured after two trial weeks and two weeks after permanent implantation when stimulation is turned off. This may provide insight into the rapid effects of SCS on the CRPS mechanisms and whether these differ from several months of SCS.

To further determine the effect of SCS on vasomotor disturbances, the histogram features of the thermographic images should be combined in a machine-learning model. For the CPM and TS, a protocol could clearly define what needs to be done each time per test. For the CPM, a test round can also be performed during the ice water, so there are three moments to compare. With the TS, it is essential to determine what to do if the prick is considered too painful. In current patients, there is no inflammation, which is now believed to be absent. However, it may be suppressed or present peripherally, which is more invasive to determine. To improve the assessment of the activity, the duration or intensity of the activity could be evaluated.

During stimulation, electrophysical data related to the stimulation and ECAP recordings are stored on the IPG. These data could be used to evaluate the specific settings of the SCS and if there is a relationship with the improvement of symptoms. For example, the data include the most commonly used current and whether the stimulation is within the window for the ECAPs to be measured. These data can also help determine how the closed-loop system performs compared to the open-loop system.

## 5.3 Conclusion

### 5.3.1 Conclusion Thermographic Images FR-study

Thermographic image histogram features of patients with and without vasomotor improvement were analyzed based on the change in differences between affected and unaffected extremities after 3 months of SCS. The difference between the left and right extremities showed a decrease in the histogram features mean, median, maximum, peak and quartile range after three months of SCS in patients with improved vasomotor symptoms. This is consistent with the hypothesis linking it to an improvement of vasomotor disturbances. Especially in patients with cold CRPS  a decrease was observed in the mean, median and quartile values of the histogram for patients with improved vasomotor symptoms after three months of SCC. The initial results seem promising for quantifying vasomotor disturbances based on thermographic images

### 5.3.2 Conclusion CL-study

Even though these are preliminary results, SCS improved symptoms of vasomotor disturbances and CNS dysregulation, as well as the activity of the evaluated patients. Compared to the improvement of the symptoms according to the CSS results, it is also possible to establish an improvement of the symptoms using the histogram features of the thermographic images, the CPM test and tracking the step counts. All patients indicated that they preferred the closed-loop setting. In addition, the results of CSS, CPM and the histogram features of the thermographic images show symptom improvement to a greater extent for closed-loop SCS than for open-loop SCS.

# Reference


1. Bruehl S. Complex regional pain syndrome. BMJ [Internet]. 2015;351. Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L606006167&from=export http://dx.doi.org/10.1136/bmj.h2730
2. Goebel A, Birklein F, Brunner F, Clark JD, Gierthmühlen J, Harden N, et al. The Valencia consensus-based adaptation of the IASP complex regional pain syndrome diagnostic criteria. Pain [Internet]. 2021 Sep 1 [cited 2022 May 16];162(9):2346–8. Available from: /pmc/articles/PMC8374712/
3. Huygen FJPM, Kleef M van, Vissers KCP, Zuurmond WWA. Handboek pijngeneeskunde. De Tijdstroom; 2014.
4. Birklein F, Handwerker HO. Complex regional pain syndrome: How to resolve the complexity? Pain [Internet]. 2001;94(1):1–6. Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L32907552&from=export http://dx.doi.org/10.1016/S0304-3959(01)00393-1
5. Birklein F, Schlereth T. Complex regional pain syndrome-significant progress in understanding. Pain [Internet]. 2015 Apr 1 [cited 2021 Sep 22];156(4):S94–103. Available from: https://pubmed.ncbi.nlm.nih.gov/25789441/
6. Caylor J, Reddy R, Yin S, Cui C, Huang M, Huang C, et al. Spinal cord stimulation in chronic pain: evidence and theory for mechanisms of action. Bioelectron Med [Internet]. 2019 Jun 28 [cited 2022 Apr 29];5(1):1–41. Available from: https://link.springer.com/articles/10.1186/s42234-019-0023-1
7. Mangnus TJP, Bharwani KD, Dirckx M, Huygen FJPM. From a Symptom-Based to a Mechanism-Based Pharmacotherapeutic Treatment in Complex Regional Pain Syndrome. Drugs 2022 825 [Internet]. 2022 Mar 5 [cited 2022 May 2];82(5):511–31. Available from: https://link.springer.com/article/10.1007/s40265-022-01685-4
8. Misidou C, Papagoras C. Complex regional pain syndrome: An update. Mediterr J Rheumatol [Internet]. 2019;30(1):16–25. Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L627636492&from=export http://dx.doi.org/10.31138/mjr.30.1.16
9. Deer TR, Grider JS, Lamer TJ, Pope JE, Falowski S, Hunter CW, et al. A systematic literature review of spine neurostimulation therapies for the treatment of pain. Pain Med (United States) [Internet]. 2020 Jul 1 [cited 2022 Jul 4];21(7):1421–32. Available from: https://academic-oup-com.eur.idm.oclc.org/painmedicine/article/21/7/1421/5731305
10. Kemler MA, De Vet HCW, Barendse GAM, Van Den Wildenberg FAJM, Van Kleef M. Effect of spinal cord stimulation for chronic complex regional pain syndrome Type I: Five-year final follow-up of patients in a randomized controlled trial. J Neurosurg [Internet]. 2008 Feb 1 [cited 2021 Nov 23];108(2):292–8. Available from: https://thejns-org.eur.idm.oclc.org/view/journals/j-neurosurg/108/2/article-p292.xml
11. Taylor RS. Spinal Cord Stimulation in Complex Regional Pain Syndrome and Refractory Neuropathic Back and Leg Pain/Failed Back Surgery Syndrome: Results of a Systematic Review and Meta-Analysis. J Pain Symptom Manage. 2006 Mar 1;31(4 SUPPL.):S13–9.
12. Geurts JW, Smits H, Kemler MA, Brunner F, Kessels AGH, Van Kleef M. Spinal cord stimulation for complex regional pain syndrome type I: A prospective cohort study with long-term follow-up. Neuromodulation. 2013 Nov 1;16(6):523–9.
13. Deer TR, Mekhail N, Provenzano D, Pope J. The appropriate use of neurostimulation of the spinal cord and peripheral nervous system for the treatment of chronic pain and ischemic diseases: the neuromodulation appropriateness consensus committee. … Technol … [Internet]. 2014; Available from: https://www.sciencedirect.com/science/article/pii/S1094715914601239
14. Parker JL, Karantonis DM, Single PS, Obradovic M, Cousins MJ. Compound action potentials recorded in the human spinal cord during neurostimulation for pain relief. Pain. 2012 Mar 1;153(3):593–601.
15. Birklein F, Ajit SK, Goebel A, Perez RSGM, Sommer C. Complex regional pain syndrome-phenotypic characteristics and potential biomarkers. Nat Rev Neurol [Internet]. 2018 Mar 16 [cited 2022 Jul 13];14(5):272–84. Available from: https://www-nature-com.eur.idm.oclc.org/articles/nrneurol.2018.20
16. Holzer P. Peptidergic sensory neurons in the control of vascular functions: mechanisms and significance in the cutaneous and splanchnic vascular beds. [Internet]. Vol. 121, Reviews of physiology, biochemistry

and pharmacology. Rev Physiol Biochem Pharmacol; 1992 [cited 2021 Nov 9]. p. 49–146. Available from: https://pubmed.ncbi.nlm.nih.gov/1485073/

17. Kortekaas MC, Niehof SP, Stolker RJ, Huygen FJPM. Pathophysiological Mechanisms Involved in Vasomotor Disturbances in Complex Regional Pain Syndrome and Implications for Therapy: A Review. Pain Pract. 2016;16(7):905–14.
18. Coderre TJ, Bennett GJ. A hypothesis for the cause of complex regional pain syndrome-type I (reflex sympathetic dystrophy): Pain due to deep-tissue microvascular pathology. Pain Med (United States) [Internet]. 2010 Aug 1 [cited 2022 Jul 13];11(8):1224–38. Available from: https://academic-oup-com.eur.idm.oclc.org/painmedicine/article/11/8/1224/1856104
19. Wasner G. Vasomotor disturbances in complex regional pain syndrome-A review. Pain Med (United States) [Internet]. 2010 Aug 1 [cited 2021 Sep 22];11(8):1267–73. Available from: https://academic.oup.com/painmedicine/article/11/8/1267/1856849
20. Okumo T, Takayama Y, Maruyama K, Kato M, Sunagawa M. Senso-Immunologic Prospects for Complex Regional Pain Syndrome Treatment. Front Immunol. 2022;12.
21. Lundeland B, Toennis M, Züchner M, Janerås L, Stubhaug A, Hansson P. Spinal cord stimulation for the treatment of peripheral neuropathic pain. Tidsskr Den Nor legeforening [Internet]. 2021 Jun 2 [cited 2022 Aug 5];141(9). Available from: https://tidsskriftet.no/en/2021/06/klinisk-oversikt/spinal-cord-stimulation-treatment-peripheral-neuropathic-pain
22. Kemler MA, Reulen JPH, Barendse GAM. Impact of spinal cord stimulation on sensory characteristics in complex regional pain syndrome type I: a randomized trial. J … [Internet]. 2001; Available from: https://pubs.asahq.org/anesthesiology/article-abstract/95/1/72/39067
23. Visnjevac O, Costandi S, Patel BA, Azer G, Agarwal P, Bolash R, et al. A Comprehensive Outcome-Specific Review of the Use of Spinal Cord Stimulation for Complex Regional Pain Syndrome. Pain Pract [Internet]. 2017 Apr 1 [cited 2022 Jul 4];17(4):533–45. Available from: https://onlinelibrary-wiley-com.eur.idm.oclc.org/doi/full/10.1111/papr.12513
24. Melzack R, Wall PD. Pain mechanisms: A new theory. Science (80- ) [Internet]. 1965 Nov 19 [cited 2022 May 16];150(3699):971–9. Available from: https://www.science.org/doi/abs/10.1126/science.150.3699.971
25. Parker JL, Karantonis DM, Single PS, Obradovic M, Laird J, Gorman RB, et al. Electrically evoked compound action potentials recorded from the sheep spinal cord. Neuromodulation. 2013 Aug 1;16(4):295–303.
26. Guan Y. Spinal cord stimulation: Neurophysiological and neurochemical mechanisms of action. Curr Pain Headache Rep [Internet]. 2012 Jun 8 [cited 2022 Apr 29];16(3):217–25. Available from: https://link.springer.com/article/10.1007/s11916-012-0260-4
27. Kriek N, Schreurs MWJ, Groeneweg JG, Dik WA, Tjiang GCH, Gültuna I, et al. Spinal Cord Stimulation in Patients With Complex Regional Pain Syndrome: A Possible Target for Immunomodulation? Neuromodulation [Internet]. 2017;21(1):77–86. Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L620278361&from=export http://dx.doi.org/10.1111/ner.12704
28. Niehof SP, Huygen FJPM, van der Weerd RWP, Westra M, Zijlstra FJ. 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 [Internet]. 2006 May 12 [cited 2021 Sep 1];5. Available from: https://pubmed.ncbi.nlm.nih.gov/16689997/
29. Song J, Yin Y, Wang H, Chang Z, Liu Z, Cui L. A review of original articles published in the emerging field of radiomics. Eur J Radiol. 2020 Jun 1;127:108991.
30. Starmans MPA, van der Voort SR, Tovar JMC, Veenland JF, Klein S, Niessen WJ. Radiomics. In: Handbook of Medical Image Computing and Computer Assisted Intervention. Academic Press; 2019. p. 429–56.
31. Starmans MPA, van der Voort SR, Phil T, Timbergen MJM, Vos M, Padmos GA, et al. Reproducible radiomics through automated machine learning validated on twelve clinical applications. 2021 Aug 19 [cited 2022 Nov 26]; Available from: https://arxiv.org/abs/2108.08618v2
32. Starmans M, Van der Voort S, Phil T, Klein S. Workflow for Optimal Radiomics Classification (WORC). . Available via h. Accessed [Internet]. Zenodo. 2018 [cited 2022 Aug 1]. Available from: https://github.com/MStarmans91/WORC

33. Mostert M, Huygen FJPM, Bijl EJ, Vos CCD, Starmans MPA. Objective Analysis of Vasomotor Disturbances in CRPS: Automatic Segmentation and Classification of Thermography Images. 2020;
34. Bijl* EJ, Starmans* MPA, Mostert JM, Klein S, Huygen FJPM, Vos CC de. Automatic quantification of complex regional pain syndrome using radiomics and deep learning based on thermography images. In Preperation.
35. Mironer YE, Somerville JJ. Pain Tolerance Threshold: A Pilot Study of an Objective Measurement of Spinal Cord Stimulator Trial Results. Pain Med [Internet]. 2000 Jun 1 [cited 2022 Jul 4];1(2):110–5. Available from: https://academic-oup-com.eur.idm.oclc.org/painmedicine/article/1/2/110/1816546
36. Sankarasubramanian V, Chiravuri S, Mirzakhalili E, Anaya CJ, Scott JR, Brummett CM, et al. Quantitative Sensory Testing of Spinal Cord and Dorsal Root Ganglion Stimulation in Chronic Pain Patients. Neuromodulation [Internet]. 2021 Jun 1 [cited 2022 Apr 29];24(4):672–84. Available from: www.neuromodulationjournal.com
37. Eide PK. Wind-up and the NMDA receptor complex from a clinical perspective. Eur J Pain [Internet]. 2000 Mar 1 [cited 2022 Jul 4];4(1):5–15. Available from: https://onlinelibrary-wiley-com.eur.idm.oclc.org/doi/full/10.1053/eujp.1999.0154
38. Yarnitsky D, Arendt-Nielsen L, Bouhassira D, Edwards RR, Fillingim RB, Granot M, et al. Recommendations on terminology and practice of psychophysical DNIC testing. Eur J Pain [Internet]. 2010 Apr 1 [cited 2022 Jul 4];14(4):339–339. Available from: https://onlinelibrary-wiley-com.eur.idm.oclc.org/doi/full/10.1016/j.ejpain.2010.02.004
39. Kriek N, de Vos CC, Groeneweg JG, Baart SJ, Huygen FJPM. Allodynia, Hyperalgesia, (Quantitative) Sensory Testing and Conditioned Pain Modulation in Patients With Complex Regional Pain Syndrome Before and After Spinal Cord Stimulation Therapy. Neuromodulation. 2022 Aug 30;
40. Bharwani KD, Dirckx M, Stronks DL, Dik WA, Schreurs MWJ, Huygen FJPM. Elevated Plasma Levels of sIL-2R in Complex Regional Pain Syndrome: A Pathogenic Role for T-Lymphocytes? Mediators Inflamm. 2017;2017.
41. Harden RN, Bruehl S, Perez RSGM, Birklein F, Marinus J, Maihofner C, et al. Validation of proposed diagnostic criteria (the "budapest Criteria") for Complex Regional Pain Syndrome. Pain. 2010 Aug 1;150(2):268–74.
42. Kriek N, Groeneweg JG. Comparison of tonic spinal cord stimulation, high-frequency and burst stimulation in patients with complex regional pain syndrome: a double-blind, randomised placebo controlled trial. Bmc …. 2015;
43. Kriek N, Groeneweg JG, Stronks DL, de Ridder D, Huygen FJPM. Preferred frequencies and waveforms for spinal cord stimulation in patients with complex regional pain syndrome: A multicentre, double-blind, randomized and placebo-controlled crossover trial. Eur J Pain (United Kingdom) [Internet]. 2017 Mar 1 [cited 2022 May 13];21(3):507–19. Available from: https://onlinelibrary-wiley-com.eur.idm.oclc.org/doi/full/10.1002/ejp.944

# Appendix A

The segmentation steps of the thermographic images for one patient. **Figure *19*** shows at **a.** the rotated NifTi image with next to it the initial mask obtained with the trained U-net model. As is visible the segmentation is not perfect and when splitting in **Figure *20*** some parts are missing. Therefore the masks are corrected with ITK-Snap shown in **Figure *21***. The original thermograph with the adapted segmentations are visualized in **Figure *22***.

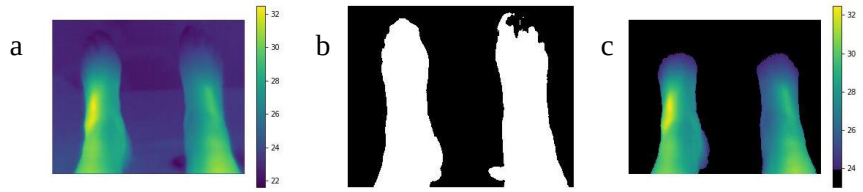


**Figure 19**. a. NifTi image of one patient in FR-study b. corresponding segmentation c. Segmentation form NifTi image and mask combined.

**Figure 20**. Left and right mask after splitting the original mask

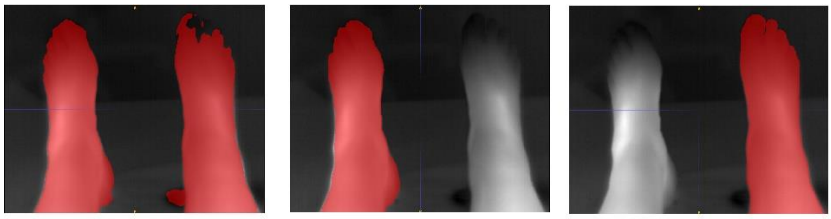

**Figure 21**. Corrected masks from both left and right using ITK snap

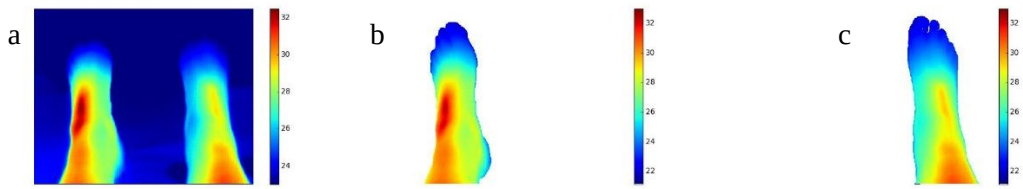


**Figure 22**. Final segmentation of both left and right part by combining the image with the corrected masks.

## 5.4 Differences between affected extremities

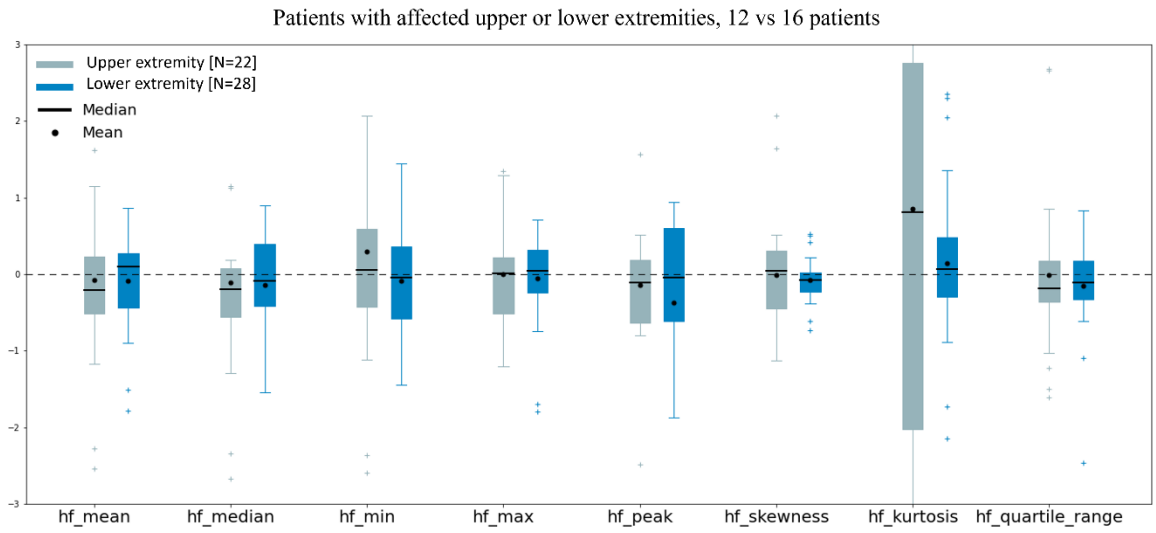


**Figure 1.** Differences in histogram feature values between G0 and G1 for thermographic images of patients with affected upper (N=22) or lower extremities (N=28).

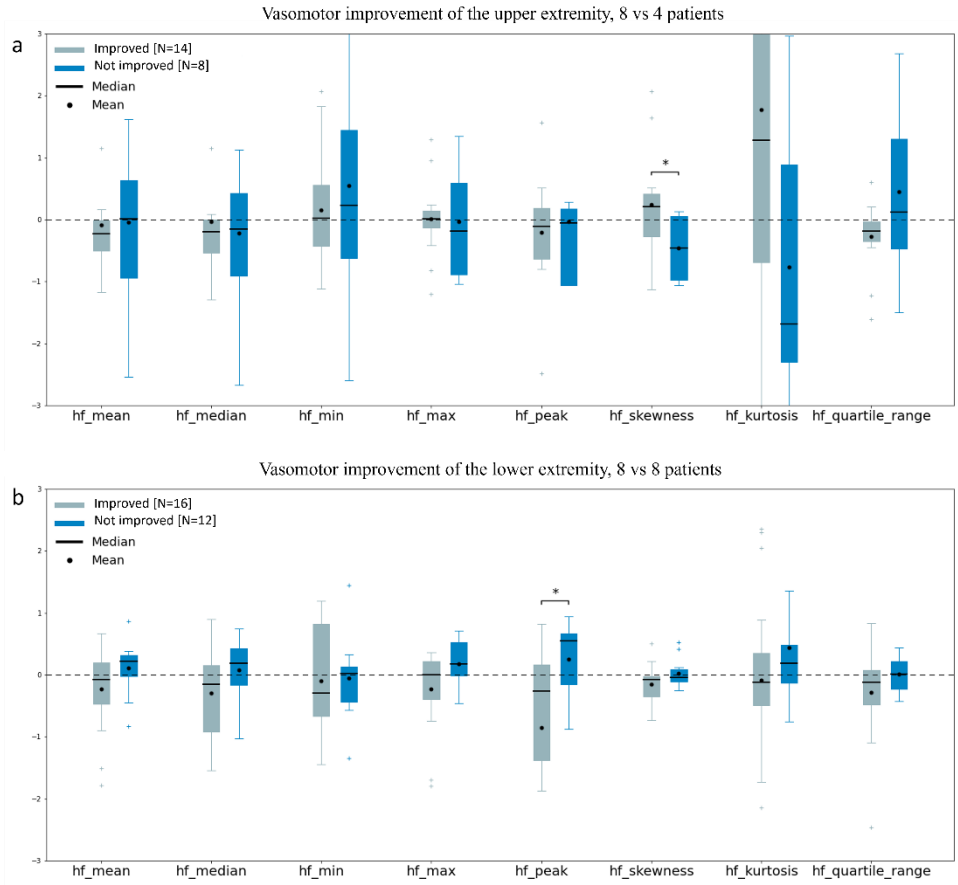


**Figure 2.** changes between G0 and G1 per histogram features for thermographic images of patients with improved and without improved vasomotor symptoms, for the **a.** upper and **b.** lower extremities.
* statistically significant

## 5.5 Differences between CRPS type

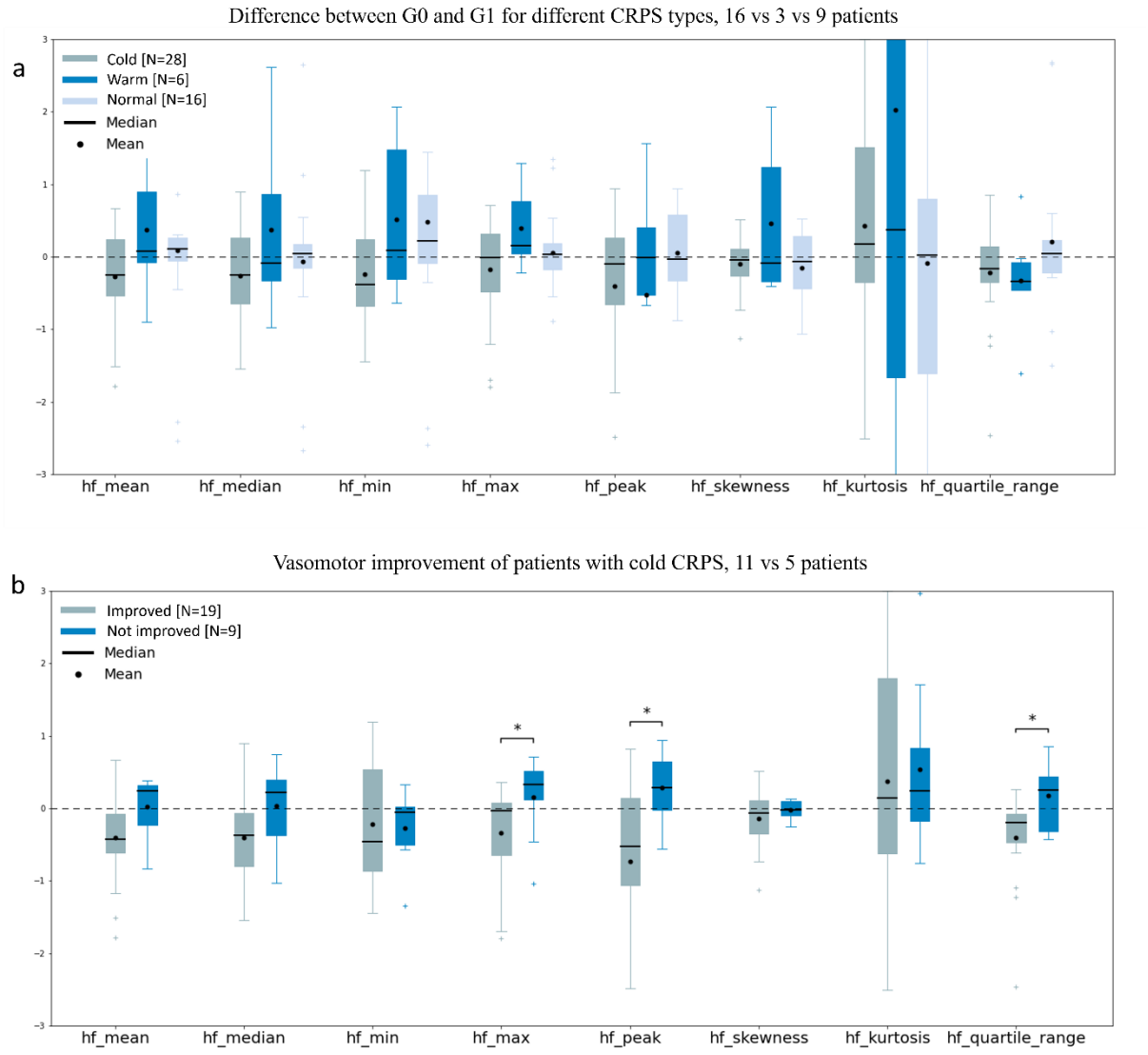


**Figure 3. a**. changes between G0 and G1 per histogram for thermographic images of patients with cold, warm and normal CRPS, established by the physician at G0. **b.** changes between G0 and G1 per histogram for patients with cold CRPS.
* statistically significant

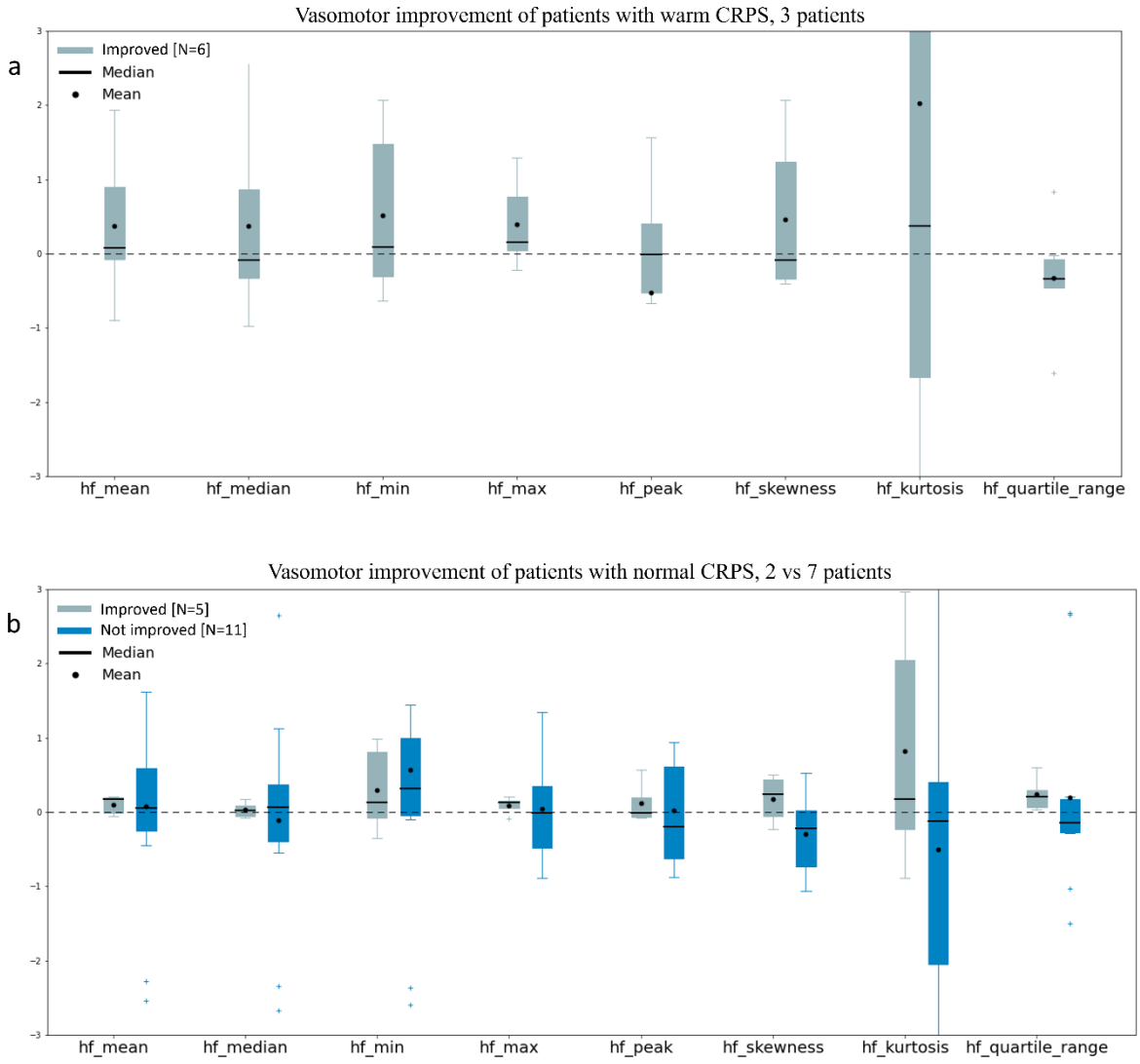


**Figure 4. a**. changes between G0 and G1 per histogram for thermographic images of patients with warm CRPS. **b.** changes between G0 and G1 per histogram for patients with normal CRPS.

**Table 5**.Difference between G0 and G1 for all histogram features for patients with vasomotor improvement

| | Mean | Median | Minimum | Maximum | Peak | Quartile Range | Skewness | Kurtosis | Standard deviation | Peak position | Range | Energy | Entropy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| HF11_feet | -0.09 | -0.11 | 1.11 | 0.03 | -0.65 | -0.29 | -0.35 | 0.89 | -0.27 | -4 | -0.56 | 9673980.52 | 0.12 |
| HF12_lower leg | -0.89 | -0.98 | -0.25 | -0.21 | -4.53 | -0.46 | -0.38 | -0.37 | 0.08 | -12 | 0.24 | -45219068.33 | 0.08 |
| HF12_feet ankles | -0.09 | -0.38 | -0.64 | 0.07 | 0.07 | 0.83 | -0.22 | -3.45 | 0.14 | 1 | -0.71 | 1454106.76 | 0.01 |
| HF19_lower leg | -0.43 | -0.38 | 0.14 | -0.54 | -0.61 | 0.13 | 0.22 | 2.30 | -0.05 | 1 | -0.68 | -24223379.40 | -0.05 |
| HF19_feet | -0.07 | -0.19 | 1.19 | -0.34 | 0.13 | -0.15 | -0.02 | 2.35 | 0.27 | -2 | 1.53 | -5832280.42 | -0.01 |
| HF23_feet ankles | -0.44 | -0.90 | -0.64 | -0.75 | -1.87 | -2.47 | 0.05 | -0.24 | -0.95 | -4 | -1.42 | -29010758.08 | -0.44 |
| HF23_feet | -0.58 | -1.23 | -0.47 | -1.79 | -5.09 | -1.10 | -0.74 | -0.28 | -0.60 | -31 | -2.26 | -8570052.39 | -0.21 |
| HF28_feet ankles | 0.42 | 0.56 | -1.36 | 0.32 | 0.82 | -0.07 | -0.07 | 0.14 | -0.19 | -1 | 0.24 | 8307015.53 | -0.04 |
| HF28_feet | 0.67 | 0.90 | -0.74 | -0.02 | 0.26 | -0.10 | -0.01 | -0.01 | -0.02 | 2 | 0.14 | 5183049.12 | -0.04 |
| HF40_feet ankles | -1.51 | -1.37 | -1.45 | 0.36 | -1.32 | -0.61 | -0.61 | -2.15 | -0.18 | -2 | -0.24 | -18872364.13 | -0.10 |
| HF40_feet | -1.79 | -1.55 | -1.29 | -1.70 | -1.56 | -0.55 | -0.35 | -1.73 | 0.04 | -2 | 0.41 | -17102605.25 | -0.02 |
| HF10_Dorsal hand | -0.75 | -0.71 | -1.12 | -1.20 | -0.68 | -0.09 | 0.36 | 1.01 | 0.00 | -2 | -0.08 | -16133922.16 | -0.06 |
| HF10_Palmar hand | -1.18 | -1.29 | -0.46 | -0.83 | -2.48 | -0.26 | -0.45 | -0.98 | -0.08 | -7 | 0.36 | -118559.30 | -0.02 |
| HF14_Dorsal hand | -0.66 | -0.62 | -0.66 | -0.41 | -0.80 | -0.18 | 0.17 | 2.14 | 0.01 | -3 | 0.00 | 654658.54 | -0.09 |
| HF14_Palmar hand | -0.27 | -0.21 | 0.61 | -0.03 | 0.16 | -0.06 | 0.52 | 7.72 | 0.13 | 1 | 0.73 | 7564887.99 | -0.05 |
| HF16_Dorsal hand | -0.45 | -0.60 | 0.20 | -0.01 | -0.53 | 0.07 | -0.30 | 1.45 | 0.00 | 0 | 0.22 | -7320514.33 | -0.02 |
| HF18_Dorsal hand | 1.94 | 2.62 | 2.07 | 1.30 | 0.51 | -1.61 | 2.07 | 7.59 | -0.32 | -3 | 0.78 | 28833136.97 | -0.09 |
| HF18_Palmar hand | 1.15 | 1.15 | 1.83 | 0.95 | 1.57 | -0.45 | 1.64 | 9.34 | -0.08 | 9 | 0.75 | 27543666.93 | 0.00 |
| HF32_Dorsal hand | -0.38 | -0.29 | -0.99 | -0.17 | -0.17 | -0.39 | 0.33 | 3.00 | -0.20 | 0 | -0.82 | -40112914.69 | -0.07 |
| HF32_Palmar hand | -0.52 | -0.37 | -0.34 | -0.03 | -0.12 | -1.23 | -1.12 | -6.11 | -0.45 | -1 | -0.39 | -27942653.53 | -0.04 |

Differences between G0 and G1 for patients with vasomotor improvement as assessed by the physician and on thermographic images. According to the hypothesis, a decrease between G0 and G1 was expected for the histogram features. Not all features or the same features decrease per patient while vasomotor improvement has been established.

**Table 6** Difference between G0 and G1 for all histogram features for patients with vasomotor improvement according to physician or thermographic images

| | P | TG | Mean | Median | Minimum | Maximum | Peak | Quartile Range | Skewness | Kurtosis | Standard deviation | Peak position | Range | Energy | Entropy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| HF25_feet ankles | Yes | No | 0.14 | 0.14 | 0.83 | 0.34 | 0.75 | -0.34 | -0.09 | -0.01 | -0.05 | 0 | 0.49 | -15536358.70 | -0.14 |
| HF25_feet | | | 0.33 | 0.54 | 0.46 | 0.26 | -0.45 | 0.26 | -0.02 | 0.17 | -0.03 | -1 | 0.20 | -8379658.71 | -0.04 |
| HF35_knees | Yes | No | 0.17 | 0.17 | -0.35 | 0.21 | -0.08 | 0.06 | 0.50 | 2.05 | -0.02 | -5 | 0.09 | 8768960.23 | 0.00 |
| HF35_feet ankles | | | 0.21 | 0.03 | 0.81 | -0.09 | 0.57 | 0.29 | -0.06 | -0.88 | 0.04 | -1 | 0.06 | -8944258.81 | -0.02 |
| HF35_feet | | | 0.20 | -0.05 | 0.98 | 0.13 | -0.07 | 0.03 | -0.23 | -0.23 | 0.08 | -3 | 0.45 | -17785774.68 | -0.09 |
| HF29_Dorsal hand | Yes | No | -0.01 | 0.08 | 0.13 | 0.06 | -0.01 | 0.60 | 0.44 | 2.97 | 0.16 | -1 | 0.21 | 5196842.09 | 0.02 |
| HF29_Palmar hand | | | -0.06 | -0.08 | -0.08 | 0.15 | 0.19 | 0.21 | 0.24 | 0.18 | 0.00 | 3 | -0.13 | 9341957.51 | 0.03 |
| HF30_Palmar hand | Yes | No | -0.19 | -0.02 | 0.86 | 0.12 | 0.21 | -0.19 | -0.16 | -2.51 | 0.11 | 0 | 1.18 | -17004011.43 | -0.02 |
| HF42_Dorsal hand | Yes | No | 0.17 | -0.19 | 0.42 | 0.24 | -0.66 | -0.24 | -0.41 | -2.09 | -0.12 | -3 | 0.12 | 29182331.71 | 0.09 |
| HF42_Palmar hand | | | -0.03 | 0.01 | -0.33 | 0.04 | -0.09 | -0.02 | 0.04 | 1.11 | 0.01 | 1 | -0.33 | -7459138.29 | 0.02 |
| HF04_feet | No | Yes | -0.45 | -0.55 | 0.32 | -0.42 | -0.88 | 0.14 | 0.41 | -0.12 | -0.08 | 1 | -0.05 | 13141928.89 | -0.05 |
| HF13_feet | No | Yes | -0.83 | -1.03 | 0.03 | -0.46 | -0.56 | 0.41 | -0.09 | -0.18 | 0.12 | -7 | -0.44 | 11142869.50 | -0.03 |

Differences between G0 and G1 for patients with vasomotor improvement as judged by the physician or on thermographic images. The patients above the line have improvement, according to the physician, and below the line, visually seen on the thermographic images. According to the hypothesis, a decrease between G0 and G1 was expected for the histogram features. Not all features or the same features decrease in each patient while vasomotor improvement is established. P = physician, TG = thermographic images

**Table 7** Difference between G0 and G1 for all histogram features for patients without vasomotor improvement

| | Mean | Median | Minimum | Maximum | Peak | Quartile Range | Skewness | Kurtosis | Standard deviation | Peak position | Range | Energy | Entropy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| HF01_feet | 0.20 | -0.13 | 0.33 | 0.12 | 0.74 | 0.25 | -0.02 | 0.24 | 0.02 | 3 | 0.46 | -4053414.97 | -0.05 |
| HF07_feet | 0.87 | 0.55 | 1.44 | 0.53 | 0.94 | 0.21 | 0.53 | 3.60 | 0.01 | -1 | 0.11 | 2007112.35 | -0.07 |
| HF20_lower leg | 0.24 | 0.40 | 0.06 | 0.52 | 0.64 | 0.44 | 0.08 | 0.84 | 0.24 | 1 | 0.69 | -13362079.17 | -0.09 |
| HF20_feet ankles | 0.39 | 0.75 | -1.34 | 0.22 | 0.50 | -0.33 | -0.10 | 0.18 | -0.44 | -4 | -1.56 | -8590283.96 | 0.02 |
| HF20_feet | 0.26 | 0.22 | -0.56 | 0.71 | 0.94 | -0.31 | 0.12 | 0.36 | -0.43 | 1 | -1.27 | 22945953.58 | 0.16 |
| HF37_feet ankles | -0.01 | -0.25 | 0.02 | -0.01 | 0.60 | -0.21 | 0.00 | 1.36 | -0.09 | 3 | -0.18 | 8768872.81 | 0.00 |
| HF37_feet | 0.06 | -0.12 | -0.10 | -0.04 | -0.38 | -0.15 | -0.22 | 0.15 | -0.07 | 6 | -0.28 | -18520897.45 | -0.03 |
| HF38_feet ankles | 0.32 | 0.39 | -0.42 | 0.62 | -0.08 | 0.17 | -0.25 | -0.75 | 0.13 | 2 | 0.21 | 4527715.08 | 0.02 |
| HF38_feet | 0.33 | 0.51 | -0.50 | 0.33 | -0.03 | -0.42 | -0.14 | -0.56 | -0.10 | -2 | -0.17 | -2910601.94 | -0.06 |
| HF41_knees | -0.05 | 0.14 | 0.05 | 0.00 | 0.62 | -0.11 | -0.08 | 0.20 | -0.02 | 2 | 0.04 | -34366074.34 | -0.14 |
| HF08_Dorsal hand | 0.31 | 0.07 | 0.55 | 0.18 | -0.31 | -0.27 | -0.42 | -2.27 | -0.10 | -1 | -0.13 | -16317976.75 | 0.01 |
| HF08_Palmar hand | 0.25 | 0.19 | 0.49 | -0.55 | 0.13 | -0.28 | -0.51 | -2.38 | -0.01 | -2 | 0.24 | -5913735.23 | 0.03 |
| HF15_Dorsal hand | 1.63 | 1.13 | 4.12 | 1.35 | -0.19 | 2.66 | -0.97 | -1.54 | 1.24 | -9 | 2.77 | -11150939.21 | 0.03 |
| HF15_Palmar hand | 3.04 | 2.65 | 4.28 | 1.23 | 8.43 | 2.68 | 0.05 | 0.61 | 1.21 | 38 | 2.78 | 51123784.55 | 0.06 |
| HF36_Dorsal hand | -2.28 | -2.34 | -2.59 | -0.89 | -3.30 | -1.03 | -1.07 | -3.36 | -0.57 | -11 | -1.70 | -27955676.60 | 0.01 |
| HF36_Palmar hand | -2.54 | -2.67 | -2.37 | -0.88 | -5.43 | -1.50 | -1.02 | -1.82 | -0.65 | -23 | -1.48 | -42652431.95 | -0.04 |
| HF43_Dorsal hand | -0.23 | -0.37 | -0.05 | 0.38 | 0.09 | 0.85 | 0.13 | 2.96 | 0.47 | 2 | 0.68 | -15331387.97 | -0.05 |
| HF43_Palmar hand | -0.50 | -0.44 | -0.02 | -1.04 | 0.28 | 0.52 | 0.10 | 1.71 | -0.11 | -4 | -0.90 | -5095081.80 | 0.04 |

Differences between G0 and G1 for patients without vasomotor improvement. According to the hypothesis, no reduction between G0 and G1 was expected for the histogram features since there was no improvement. There is a discount for some features, which also differs in terms of features.