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Diurnal and Nocturnal Skin Temperature Regulation in Chronic Complex Regional Pain Syndrome

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Abstract: Skin temperature changes due to vasomotor disturbances are important features of complex regional pain syndrome (CRPS). Because this phenomenon has only been studied under controlled conditions, information on daily circadian variability is lacking. Also, studies in chronic CRPS patients with abnormal posturing, in which coldness of the affected extremity is more common, do not exist. We examined the response to external heating as well as circadian temperature changes over several days in the affected legs of 14 chronic CRPS patients with abnormal posturing and 17 controls. Skin temperatures were recorded hourly for 14 days using wireless sensors. Although the patients' affected extremities were significantly colder before external heating, the vasodilatory response was similar in the 2 groups. Additionally, median skin temperature differences between both legs and their variability was larger in patients than in controls during the day, but not during the night. These findings indicate that the mechanisms underlying impaired skin circulation in CRPS during daytime are reversible under certain circumstances. The large variation in skin temperature differences during the day questions the validity of using a single measurement in the diagnosis of CRPS, and our results indicate that only temperature differences >1.0°C should be considered to reflect vasomotor disturbances.

Perspective: This article shows that chronic CRPS patients have a normal vasodilatory response to external heating and that skin temperature differences between the affected and unaffected lower limbs, which were highly variable during daytime, disappeared during sleep. This indicates that part of the vasomotor regulation in these patients is still functional.

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Key words: Complex regional pain syndrome, skin temperature, thermoregulation, vasomotor disturbances.

Skin temperature changes of the affected limb are an important characteristic of complex regional pain syndrome (CRPS). In the acute phase of the syndrome the skin temperature of the affected side is commonly perceived as warmer than the nonaffected limb, whereas in the chronic phase (>6 months) the clinical presentation may reverse. However, about 20 to 30% of patients have a cold extremity from onset, and in some cases the skin temperature of the affected extremity continuously varies between cold and warm.

Skin temperature disturbances, addressed from both the patient's and clinician's perspectives, play a prominent role in the Budapest diagnostic criteria of CRPS. Little is known, however, about skin temperature variability under normal daily circumstances. Because variability of skin temperature may affect the validity and reliability of information obtained for the diagnostic criteria, knowledge of its daily behavior may contribute to improvement of the diagnostic process and eventually improve classification of patient subtypes in this heterogeneous syndrome. Additionally, little is known about nocturnal skin temperature regulation in CRPS. Because dermal
vasomotor changes are important in the circadian regulation of body heat loss and are associated with sleepiness and sleep induction.\textsuperscript{10} Information on skin temperature behavior before and during sleep in the affected extremity may aid to further clarify the pathophysiology of blood flow disturbances in CRPS.

There are some indications that abnormal posturing in CRPS is related to coldness.\textsuperscript{5} Though this may suggest a more prominently impaired thermoregulation in this subtype of the condition, proper studies on skin temperatures in these patients have not been conducted. Therefore, we examined the response to external heat perturbation as well as diurnal and nocturnal temperature variability over several days in chronic CRPS patients with an affected limb that was also characterized by abnormal posturing.

Methods

Participants

Fourteen patients with CRPS type 1 of 1 lower extremity and a disease duration of at least 6 months and 17 healthy controls were included in the study. All patients fulfilled the Budapest clinical criteria for CRPS\textsuperscript{2} and suffered from abnormal posturing—most commonly a fixed plantar flexion/inversion position of the ankle in combination with restrictions in range of motion,\textsuperscript{23} because data in the present paper were collected as part of a wider study on abnormal posturing in CRPS.\textsuperscript{23} Patients were recruited from the outpatient clinic of the neurology department of the Leiden University Medical Center. Control subjects were excluded if they suffered from peripheral vascular disease or other conditions that impaired lower limb function, based on their medical history. The study was approved by the local medical ethics committee, and informed consent was obtained from all participants.

Measurements

Two approaches were used to investigate thermoregulation of the lower limbs in patients and controls: 1) external heat perturbation and 2) long-term skin temperature registration during normal daily circumstances.

External Heat Perturbation and Effect on Skin Temperature

Skin temperatures were measured in both feet with a surface thermometer (Testo quicktemp 825-T4; Testo, Lenzkirch, Germany) while participants were sitting upright in a chair with both bare feet on the floor, after a 15-minute acclimatization period in a room of 22 to 23°C (baseline measurement [BM]). A template was used to ensure exact (re)localization of the thermometer in each participant, that is, medially at 5 locations at the dorsum of the foot, which data were averaged afterwards. Both feet were then heated in a water bath at 37 to 39°C for 5 minutes, and skin temperature was measured directly after drying (ie, after heating [AH]), as well as 15 minutes later (15mAH) in the same way. This protocol was repeated at 7, 14, and 35 days after the first measurement. Skin temperatures of each participant were averaged over these 4 time points. We also registered whether patients perceived the skin temperature of the affected side as warmer, cooler, or equal as compared to the unaffected side at the first measurement. Mean numerical rating scale (NRS) score of pain prior to baseline temperature measurement was registered in CRPS patients.

Long-Term Registration

Skin temperature data were collected for 2 weeks with thermoregistration buttons (TBs) (iButton type DS1922L; Maxim, San Jose, CA), which have been shown to be a convenient and reliable tool for this purpose.\textsuperscript{25} The TBs were directly placed on the skin above the extensor digitorum brevis muscle belly on both feet and fixed with Fixomul tape (Beiersdorf, Hamburg, Germany). This location was marked with a water-resistant marker. Skin temperature was recorded hourly with a thermal sensitivity of ±.5°C during 14 days. Participants recorded the exact time they went to bed for the night and the time they got out of bed—the time in between is referred to as “night.” All remaining temperature data are referred to as “day.” Participants also documented the periods that the TBs were removed (eg, during showering), and measurements from 15 minutes before to 15 minutes after these intervals were excluded. As no information was available on ambient temperature during the measurements, the absolute differences in skin temperatures between right and left legs (abs\textsubscript{D}RL) were calculated at all time points, and their absolute mean differences (Mabs\textsubscript{D}RL and standard deviations (SDabs\textsubscript{D}RL) for day (D) and night (N) per subject were used for comparisons between groups.

Statistical Analysis

External Heat Perturbation

Differences in skin temperatures between both groups and sides at all time points were subjected to a mixed analysis of variance, with time (BM, AH, 15mAH) and side (affected [patients]/right [controls] vs unaffected [patients]/left [controls]) as within-subject factors and with group (CRPS patients vs healthy controls) as between-subjects factor. The degrees of freedom were adjusted using the Greenhouse-Geisser estimates for the tests of within-subjects effects as the sphericity assumption was violated.\textsuperscript{6}

Long-Term Registration

As data were not normally distributed, not even after commonly used transformations, differences in Mabs\textsubscript{D}RL and SDabs\textsubscript{D}RL between groups during day and night were analyzed with Mann-Whitney U tests. To determine the optimal Mabs\textsubscript{D}RL value to discriminate between patients and controls, receiver operating characteristic curve analysis was used, where the highest sum of sensitivity and specificity (ie, Youden index) was used as the optimal cut-off point.

All statistical analyses were performed with IBM SPSS Statistics, version 20.0 (IBM Corp, Armonk, NY). P values <.05 were considered significant.
Results

Both groups included 2 males. The mean ± SD age of CRPS patients was 41.7 ± 12.8 years versus 42.0 ± 11.6 years for controls (P = .952). Mean disease duration was 123.1 ± 72.9 (range = 10–240) months. Mean NRS score for pain was 6.6 ± 2.5 (range = 4–10). All patients had abnormal posturing. In CRPS patients, sensory disturbances (symptoms/signs) were present in 100%/100%; trophic skin, nail, and/or hair growth changes in 93%/67%; changes in skin temperature and/or color in 100%/73%; edema in 67%/40%; and sweating changes in 47%/7%. Ten of the 14 patients indicated that they always perceived their affected leg as colder than the unaffected side, whereas 4 patients reported that they perceived the temperatures of their affected side as intermittently warmer and colder.

External Heating Perturbation

Skin temperatures of all lower extremities for the various time points are presented in Fig 1. The mixed analysis of variance revealed a significant main effect of time, with AH skin temperature (P < .001) and 15mAH (P < .001) being higher than the BM. Additionally, AH skin temperature was higher than 15mAH (P < .001). Also, there was a significant main effect of group: mean ± SD skin temperatures in CRPS patients were significantly lower than in controls at all time points (BM: 27.0 ± 3.0 [affected] and 28.0 ± 2.2 [unaffected] vs 29.2 ± 1.5 [right control] and 29.1 ± 1.4 °C [left control]; AH: 32.6 ± 9 [affected] and 32.9 ± 1.0 [unaffected] vs 33.8 ± 0.7 [right control] and 33.6 ± 0.5 °C [left control]; 15mAH: 30.1 ± 1.6 [affected] and 30.5 ± 1.4 [unaffected] vs 31.4 ± 0.8 [right control] and 31.1 ± 0.7 °C [left control]; P = .003). No significant main effect of side on skin temperature was found (P = .354). We also did not observe significant 2-way (ie, time × group: P = .144; side × group: P = .088) or 3-way interaction effects (time × side × group: P = .443). Compared to the unaffected side, skin temperatures of the affected side were consistently warmer in 3 patients, were colder in 6 patients, but varied in 5 CRPS patients across the 4 visits. Two of 14 patients perceived the skin temperature of their affected extremity incorrectly, that is, they perceived their affected extremity as warmer than the unaffected side.

Long-Term Registration

Values of means and SDs of the skin temperatures of both right and left lower extremities of patients and controls are shown in Table 1. Fig 2 shows circadian temperature data of 4 random days of 2 exemplary patients and 2 controls. During the day, median MabsΔRL and SDabsΔRL were significantly larger in patients than in controls (P = .015 and P = .024, respectively), whereas during the night no differences were observed (P = .427 and P = .383) (Table 2). In 2 of the 14 patients, the affected extremity was on average warmer during daytime than the unaffected side (+1.13 and +.47 °C), although these patients were convinced that their affected side was always colder. In 12 patients, the affected legs were indeed on average colder than the unaffected side (range = −.06 to −7.93 °C).

To evaluate whether the results from a randomly picked day would have led to the same results, we compared the median (interquartile range) absolute temperature differences of day 9 between groups. Similar results were found: MabsΔRL/D patients 1.04 (.77–2.01) versus controls .78 (.55–.96) °C (P = .037); SDabsΔRL/D patients .71 (.54–1.00) versus controls .54 (.44–.68) °C (P = .018); MabsΔRL/N patients .63 (.42–1.01) versus controls .59 (.47–.77) °C (P = .551); SDabsΔRN patients .55 (.35–.99) versus controls .47 (.35–.72) °C (P = .202).

Receiver operating characteristic curve analysis revealed that a MabsΔRL of 1.076 °C during daytime optimally discriminated between patients and controls, yielding a sensitivity of 76.5% and a specificity of 94.1%, with an area under the curve of .792 (Fig 3).

Figure 1. Results from the heating intervention: mean skin temperatures of both lower extremities of patients and controls per time point. Skin temperatures are significantly different between the different time points (P < .001) and between patients and controls (P = .003), but the change over time is similar for both sides in both groups.

Table 1. Mean Skin Temperatures and SDs Obtained From TBs for All Extremities

<table>
<thead>
<tr>
<th>MEASUREMENT</th>
<th>CRPS PATIENTS (N = 14)</th>
<th>CONTROLS (N = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AFFECTED</td>
<td>UNAFFECTED</td>
</tr>
<tr>
<td>Day</td>
<td>29.6 (3.0)</td>
<td>30.7 (2.2)</td>
</tr>
<tr>
<td>SD day</td>
<td>2.5 (9)</td>
<td>2.2 (6)</td>
</tr>
<tr>
<td>Night</td>
<td>33.7 (2.8)</td>
<td>34.3 (1.1)</td>
</tr>
<tr>
<td>SD night</td>
<td>2.1 (1.4)</td>
<td>1.8 (9)</td>
</tr>
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</table>

NOTE. Data are expressed as mean (SD), °C.
Discussion

This study on skin thermoregulation of chronic CRPS patients with abnormal postures revealed several important findings. First, we found that the response to external heating and subsequent cooling followed a similar pattern in both sides in patients and controls, albeit with a significantly lower baseline temperature in the patients’ affected leg, a result that corresponds to previous findings in chronic CRPS (reviewed in15). Normally, heating of the skin triggers an immediate local axon reflex-mediated vasodilation and a prolonged vasodilatory response that is dependent on both the release of vasoconstrictor sympathetic tone and increased levels of nitrous oxide.16 In our study, only the prolonged response was examined and appeared to be intact in CRPS patients. Similar findings, that is, normal vasodilation in response to external heating, were found using whole-body cooling and subsequent warming in patients with acute CRPS of whom the majority had affected upper limbs and a warm-type phenotype.21,30 Our results elaborate on those of previous studies, by showing normal vasodilatory response in chronic CRPS patients with affected lower limbs. Although in inter-mediate and

Figure 2. TB data of 4 consecutive days of 2 exemplary patients and controls. This figure shows the skin temperature (°C) for every hour of 4 consecutive days of 2 different patients (upper 2 graphs) and 2 different controls (lower 2 graphs). It clearly shows that differences between both legs are small during the night, whereas during the day differences are larger in both groups. The first patient’s affected leg is continuously colder than the unaffected leg during daytime. The second patient shows an irregular pattern: the affected side is warmer at day 1, colder at day 2, and variable at day 3. In both controls, absolute right/left differences are smaller during the night.
also been suggested that nocturnal blood flow changes are required to initiate sleep.\textsuperscript{10-12,26} Also, a skin temperature and decreased central core temperature that an associated melatonin-mediated increase in distal sleep are largely unknown, recent findings indicate processes that regulate nocturnal temperature and sympathetic downregulation has been proposed as an important feature of both processes.\textsuperscript{11} However, it has been previously demonstrated in a CRPS type II rat model.\textsuperscript{1,27} Visual inspection of the temperature data previously been demonstrated in a CRPS type II rat model.\textsuperscript{1,27} Visual inspection of the temperature data also revealed that in some patients skin temperature of the affected side could alternate between 2 subsequent measurements from 2\textdegree C colder to 3\textdegree C warmer than the unaffected side, which is consistent with previous data.\textsuperscript{13} Moreover, 14\% of patients (ie, 2 of 14) perceived their skin temperatures opposite to the value that was measured. Inconsistent findings between measured and perceived skin temperature in CRPS have been described before.\textsuperscript{22} Collectively these findings question the validity of a single skin temperature measurement in the context of the diagnosis of CRPS (with respect to both the symptom and sign level), as has been previously mentioned by others.\textsuperscript{24,30} Long-term temperature registration—or possibly measurement of skin temperature at different time points—may improve diagnostic accuracy and simultaneously provide a comprehensive view of the dynamic thermoregulatory processes that regulate nocturnal temperature and sleep-related behavior, that is, putting the lights off, relaxation, and lying down.\textsuperscript{10}

In chronic, cold-type CRPS, local vascular changes leading to vasoconstriction during the day have been described, including reduced levels of nitrous oxide and increased endothelin-1, as well as upregulation of adrenergic receptors.\textsuperscript{26} However, the presence of both normal nocturnal skin temperatures and preserved vasodilation after external heating indicate that vasoconstriction in cold-type CRPS can be overruled under certain circumstances, as has been described before.\textsuperscript{14,21,29,30}

We additionally examined whether the nocturnal increase in skin temperature of the affected side could result from external heating, that is, conduction via the unaffected side together with the thick insulating bedding, and/or occur as a response to lying down. To this end, skin temperatures of both affected and unaffected legs of 3 CRPS patients were measured using 3 TBs during a position change (ie, from sitting to supine position after patients had been seated for at least 30 minutes to acclimatize), after which they remained in supine position for 50 minutes, whereafter a thick blanket was added for another period of 50 minutes. This setup did not lead to a similar substantial and relatively fast increase in skin temperatures of both affected and unaffected legs as was seen in the original TB data (Table 1, Fig 2): mean ± SD temperature differences between sitting and lying down were $0.67 \pm 1.48\textdegree C$ and did not differ between affected and unaffected sides, whereas adding a blanket to the already supine participants increased skin temperatures of both sides by $0.33 \pm 0.54\textdegree C$. Apparently, other factors than position change and the insulating bedding must play a role in our findings. Possibly, edema—which can hamper the vascular heat release to the skin and is usually more evident in an upright position—may have contributed to the skin temperature differences between day and night.

Third, this study shows a conspicuously larger daytime variation in absolute skin temperature differences between the lower limbs in CRPS patients compared to controls. Similar large temperature variability has previously been demonstrated in a CRPS type II rat model.\textsuperscript{1,27} Visual inspection of the temperature data also revealed that in some patients skin temperature of the affected side could alternate between 2 subsequent measurements from $2\textdegree C$ colder to $3\textdegree C$ warmer than the unaffected side, which is consistent with previous data.\textsuperscript{13} Moreover, 14\% of patients (ie, 2 of 14) perceived their skin temperatures opposite to the value that was measured. Inconsistent findings between measured and perceived skin temperature in CRPS have been described before.\textsuperscript{22} Collectively these findings question the validity of a single skin temperature measurement in the context of the diagnosis of CRPS (with respect to both the symptom and sign level), as has been previously mentioned by others.\textsuperscript{24,30} Long-term temperature registration—or possibly measurement of skin temperature at different time points—may improve diagnostic accuracy and simultaneously provide a comprehensive view of the dynamic thermoregulatory

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<th>CONTROLS (n = 17)</th>
<th>P</th>
<th>VALUE</th>
</tr>
</thead>
<tbody>
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<td>Day</td>
<td>1.17 (.69–1.77)</td>
<td>.88 (.61–.98)</td>
<td>.015</td>
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<tr>
<td>SD day</td>
<td>.89 (.67–1.32)</td>
<td>.65 (.57–.83)</td>
<td>.024</td>
<td></td>
</tr>
<tr>
<td>Night</td>
<td>.76 (.51–1.00)</td>
<td>.65 (.53–.81)</td>
<td>.427</td>
<td></td>
</tr>
<tr>
<td>SD night</td>
<td>.71 (.52–.82)</td>
<td>.54 (.48–.82)</td>
<td>.383</td>
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</table>

NOTE. Data are expressed as medians (interquartile range), °C.
control and disturbances in a single patient. Our data show that registration during 1 regular day is sufficient to detect significant skin temperature differences between CRPS patients and controls, and that the best discriminative value as revealed by the receiver operating characteristic curve analysis (ie, a skin temperature difference of 1.076°C) is consistent with the minimal difference that is required to score vasomotor disturbances as a sign according to the CRPS criteria (ie, 1.0°C).8 Our findings once more emphasize that temperature differences below this value should be considered as normal fluctuations and not as a specific sign or symptom of CRPS.

Disturbances of thermoregulation in CRPS have been extensively studied, and a multifactorial pathophysiology seems beyond dispute. Local vascular endothelial changes, both functional and structural, as well as disuse, may lead to a cold skin in affected extremities,8 whereas predominantly inflammatory-like changes give rise to a warm skin in CRPS.2,28 Additionally, a key role in the thermoregulatory dysfunction in CRPS is played by the central nervous system. Recent studies have provided evidence for complex interrelationships between cortical maps of space and body temperature regulation in CRPS, as the position of the affected limb in external space in relation to the body midline showed to influence skin temperatures.17-19 Furthermore, interactions between central pain and autonomic pathways were demonstrated in a study where ambiguous visual stimuli led to asymmetric vasomotor responses between CRPS affected and unaffected extremities and to an increase of pain at the affected side.4 Collectively, these findings indicate direct links between central spatial areas and disturbed thermoregulatory control as well as between pain and autonomic pathways in CRPS. The changes in skin temperatures that occurred before and during sleep in our study are likely also regulated by central pathways, but the exact mechanisms are still unclear.

This study has some potential limitations. First, we did not record ambient temperatures during the 2 weeks of registration, and no data were available on activity of extremities. However, by using the absolute differences between both legs, this problem, to some extent, was bypassed. Also, the matched controls were measured in the same period of the year as the patients, which ensured that the observed differences were not due to differences in ambient temperatures between groups. Second, it is known that temperature differences in CRPS-affected extremities can best be provoked by high to medium level of vasoconstrictor activity,29 which we could not control for during this study. However, we can deduce from the TB data that in all patients, even on the unaffected side, skin temperature fell below 25°C for several hours during this 2-week period, and rose to minimally 34°C during nights, so it seems that both high and low temperature limits have been reached. Third, all patients in our study suffered from abnormal posturing, as this was 1 of the inclusion criteria. Therefore we cannot generalize our results to CRPS patients without this feature. Fourth, the measurement error of the TB is relatively large (5°C); however, the amount of data likely compensates this sufficiently, and because this error works in both directions (higher/lower), this effect is likely annulled. Finally, the setting of this study did not allow distinguishing between the effects of “going to bed” and “falling asleep” on temperature regulation, which could have limited the number of potential explanations for the results we observed.

Recommendations and Clinical and Research Perspectives

Our data show that 1 day of registration is sufficient to capture significant skin temperature differences between CRPS patients and controls. Moreover, it adds valuable information on skin temperature variability in each patient. We therefore recommend to use TB measurements during 1 day in the diagnostic process of CRPS, or to use at least multiple skin temperature measurements during the day. If the latter procedure is followed, it is recommended that measurements are performed with the patient in an upright position with the feet hanging down, because in this position the largest differences are found.

For future studies, it would be of additional value to register the exact time a person falls asleep and the exact sleep-episode, instead of going to bed only. It would also be interesting to examine more precisely and in a larger sample size whether and to which extent the influence of position (from supine to upright, with or without limbs hanging down) would induce skin temperature changes.

In conclusion, our findings on skin temperatures in affected lower limbs of chronic CRPS patients show that the apparent mechanisms underlying sustained vasoconstriction in “cold” CRPS during the day are reversible or may be compensated by local heating as well as processes that mediate sleep. This indicates that part of the vasomotor regulation in these chronic patients is still functional. Also, long-term registration yielded a comprehensive view of the dynamic thermoregulatory control in single patients, but it also showed a high variation in skin temperatures. The latter questions the validity of a single temperature measurement as is currently used in the diagnosis of CRPS.

References

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