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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.***

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).[28] 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.[28] However, about 20 to 30% of patients have a cold extremity from onset,[3,15] and in some cases the skin temperature of the affected extremity continuously varies between cold and warm.[13,30]

Skin temperature disturbances, addressed from both the patient's and clinician's perspectives, play a prominent role in the Budapest diagnostic criteria of CRPS.[9] 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,[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.

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There are some indications that abnormal posturing in CRPS is related to coldness.[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[9] and suffered from abnormal posturing—most commonly a fixed plantar flexion/inversion position of the ankle in combination with restrictions in range of motion,[20] because data in the present paper were collected as part of a wider study on abnormal posturing in CRPS.[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.[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 (absΔRL) were calculated at all time points, and their absolute mean differences (MabsΔRL) and standard deviations (SDabsΔRL) 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.[6]

Long-Term Registration

As data were not normally distributed, not even after commonly used transformations, differences in MabsΔRL and SDabsΔRL between groups during day and night were analyzed with Mann-Whitney U tests. To determine the optimal MabsΔRL 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 ± .7 [right control] and 33.6 ± .5°C [left control]; 15mAH: 30.1 ± 1.6 [affected] and 30.5 ± 1.4 [unaffected] vs 31.4 ± .8 [right control] and 31.1 ± .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); SDabsΔRL/N patients .55 (.35–.99) versus controls .47 (.35–.72)°C (P = .202).

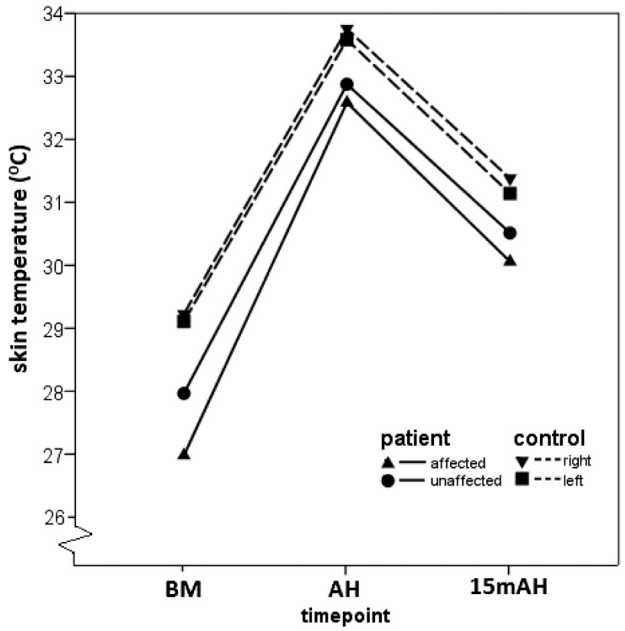

Figure 1. Results from the heating intervention: mean skin temperatures of both lower extremities of patients and controls per time point. Skin temperatures are significantly different between the different time points (P < .001) and between patients and controls (P = .003), but the change over time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

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).

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

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

	CRPS Patients (n = 14)		Controls (n = 17)	
Measurement	Affected	Unaffected	Right	Left
Day	29.6 (3.0)	30.7 (2.2)	30.8 (1.0)	31.0 (.8)
SD day	2.5 (.9)	2.2 (.6)	2.2 (.4)	2.2 (.4)
Night	33.7 (2.8)	34.3 (1.1)	34.6 (.4)	34.6 (.5)
SD night	2.1 (1.4)	1.8 (.9)	1.4 (.5)	1.3 (.5)

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

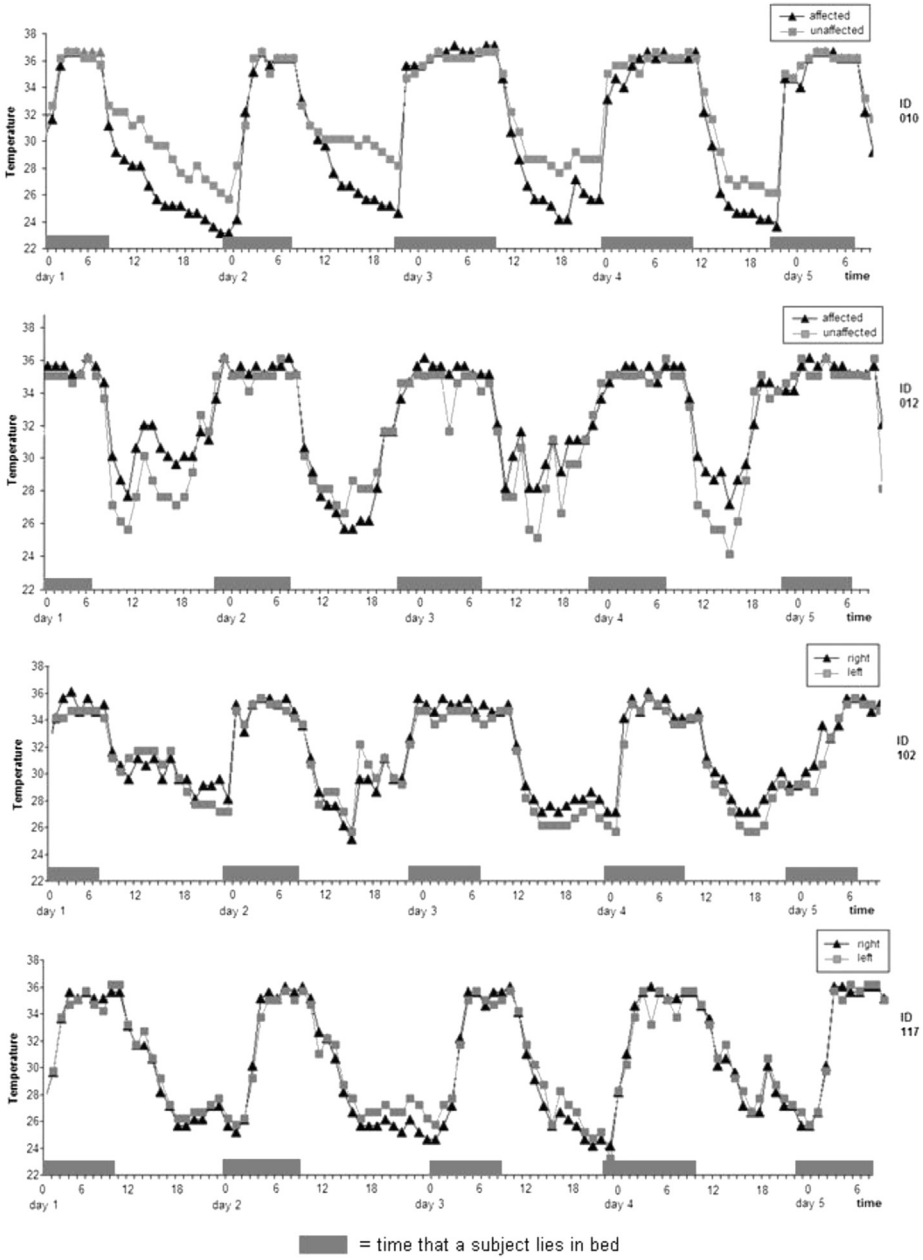

Figure 2. TB data of 4 consecutive days of 2 exemplary patients and controls. This figure shows the skin temperature (°C) for every hour of 4 consecutive days of 2 different patients (upper 2 graphs) and 2 different controls (lower 2 graphs). It clearly shows that differences between both legs are small 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.

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 in[15]). 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 intermediate and chronic CRPS patients reduced (vasodilatory) nitrous oxide and increased (vasoconstrictive) endothelin-1 concentrations have been found,[7] it appears that these disturbances may be reversible, or can be compensated by other factors when external heat is applied.

Table 2. Mean Absolute Skin Temperature Differences Obtained Via TBs Between Affected and Unaffected (Patients), or Right and Left (Controls) Legs

Measurement	CRPS Patient (n = 14)	Controls (n = 17)	P Value
Day	1.17 (.69–1.77)	.88 (.61–.98)	.015
SD day	.89 (.67–1.32)	.65 (.57–.83)	.024
Night	.76 (.51–1.00)	.65 (.53–.81)	.427
SD night	.71 (.52–.82)	.54 (.48–.82)	.383

NOTE. Data are expressed as medians (interquartile range), °C.

Second, this study shows that in contrast to the observations obtained during the day, absolute temperature differences between both legs during the night were similar in patients and controls. This implies preserved normal nocturnal thermoregulatory control in affected lower limbs of chronic CPRS patients. Our findings of nocturnal skin temperatures are in line with those of other studies on temperature regulation prior to and during sleep in healthy subjects.[12,25,26] Though the processes that regulate nocturnal temperature and sleep are largely unknown, recent findings indicate that an associated melatonin-mediated increase in distal skin temperature and decreased central core temperature are required to initiate sleep.[10-12,26] Also, a sympathetic downregulation has been proposed as an important feature of both processes.[11] However, it has also been suggested that nocturnal blood flow changes may not be related to processes that mediate sleep per se, but rather result from sleep related behavior, that is, putting the lights off, relaxation, and lying down.[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.[28] 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.[14,21,29,30]

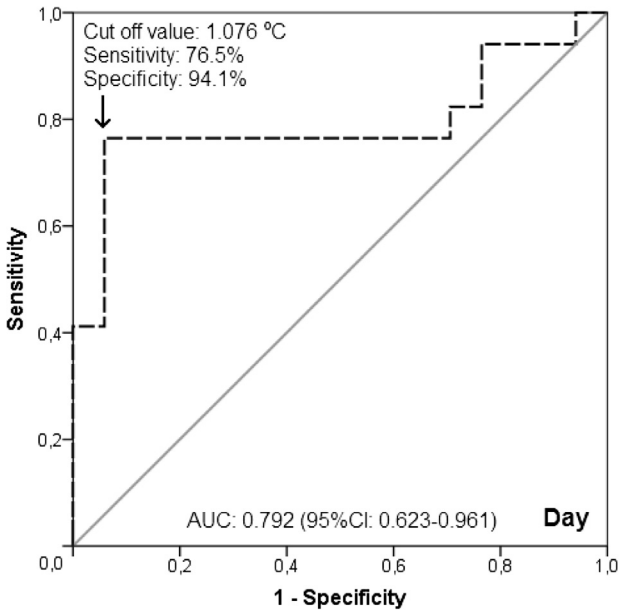

Figure 3. Receiver operating characteristic curve for the diurnal TB temperature data to discriminate patients from controls. Abbreviations: AUC, area under the curve; CI, confidence interval.

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 .67 ± 1.48°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 .33 ± .54°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.[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° colder to 3°C warmer than the unaffected side, which is consistent with previous data.[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.[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.[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 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).[9] 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,[8,28] 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,[30] 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

1. Bennett GJ, Ochoa JL: Thermographic observations on rats with experimental neuropathic pain. Pain 45:61-67, 1991

2. Birklein F, Kingery WS: Complex regional pain syndrome: A loss of inhibition? Pain 142:177-178, 2009

3. Bruehl S, Harden RN, Galer BS, Saltz S, Backonja M, Stanton-Hicks M: Complex regional pain syndrome: Are there distinct subtypes and sequential stages of the syndrome? Pain 95:119-124, 2002

4. Cohen HE, Hall J, Harris N, McCabe CS, Blake DR, Jänig W: Enhanced pain and autonomic responses to ambiguous visual stimuli in chronic complex regional pain syndrome (CRPS) type I. Eur J Pain 16:182-195, 2012

5. Eberle T, Doganci B, Krämer HH, Geber C, Fechir M, Magerl W, Birklein F: Warm and cold complex regional pain syndromes: Differences beyond skin temperature? Neurology 72:505-512, 2009

6. Field A: Discovering Statistics Using SPSS. London, Sage Publications, 2009

7. Groeneweg JG, Antonissen CH, Huygen FJPM, Zijlstra FJ: Expression of endothelial nitric oxide synthase and endothelin-1 in skin tissue from amputated limbs of patients with complex regional pain syndrome. Mediators Inflamm: 680981, http://dx.doi.org/10.1155/2008/680981, 2008

8. Groeneweg G, Huygen FJPM, Coderre TJ, Zijlstra FJ: Regulation of peripheral blood flow in complex regional pain syndrome: Clinical implication for symptomatic relief and pain management. BMC Musculoskelet Disord 10:116-128, 2009

9. Harden RN, Bruehl S, Perez RSGM, Birklein F, Marinus J, Maihofner C, Lubenow T, Buvanendran A, Macky S, Graciosa J, Mogilevski M, Ramsden C, Chont M, Vatine J-J: Validation of proposed diagnostic criteria (the "Budapest criteria") for complex regional pain syndrome. Pain 150: 268-274, 2010

10. Kräuchi K: The human sleep-wake cycle reconsidered from a thermoregulatory point of view. Physiol Behav 90: 236-245, 2007

11. Kräuchi K, Cajochen C, Wirz-Justice A: Thermophysiologic aspects of the three-process-model of sleepiness regulation. Clin Sports Med 24:287-300, 2005

12. Kräuchi K, de Boer T: Body temperature, sleep, and hibernation, in Kryger MH, Roth T, Dement WC (eds): Principles and Practice of Sleep Medicine, 5th ed. St. Louis, Elsevier Health Sciences, 2010, pp 323-334

13. Krumova EK, Frettlöh J, Klauenberg S, Richter H, Wasner G, Maier C: Long-term skin temperature measurements—A practical diagnostic tool in complex regional pain syndrome. Pain 140:8-22, 2008

14. Kurvers HA, Jacobs MJ, Beuk RJ, van den Wildenberg FA, Kitslaar PJ, Slaaf DW, Reneman RS: The influence of local skin heating and reactive hyperaemia on skin blood flow abnormalities in patients with reflex sympathetic dystrophy (RSD). Eur J Clin Invest 25:346-352, 1995

15. Marinus J, Moseley GL, Birklein F, Baron R, Maihöfner C, Kingery WS, Van Hilten JJ: Clinical features and pathophysiology of complex regional pain syndrome. Lancet Neurol 10: 637-648, 2011

16. Minson CT, Berry LT, Joyner MJ: Nitric oxide and neurally mediated regulation of skin blood flow during local heating. J Appl Physiol (1985) 91:1619-1626, 2001

17. Moseley GL, Gallace A, Iannetti GD: Spatially defined modulation of skin temperature and hand ownership of both hands in patients with unilateral complex regional pain syndrome. Brain 135:3676-3686, 2012

18. Moseley GL, Gallace A, Spence C: Bodily illusions in health and disease: Physiological and clinical perspectives and the concept of a cortical "body matrix". Neurosci Biobehav Rev 36:34-46, 2012

19. Moseley GL, Gallace A, Spence C: Space-based, but not arm-based, shift in tactile processing in complex regional pain syndrome and its relationship to cooling of the affected limb. Brain 132:3142-3151, 2009

20. Munts AG, Mugge W, Meurs TS, Schouten AC, Marinus J, Mosely GL, van der Helm FC, van Hilten JJ: Fixed dystonia in complex regional pain syndrome: A descriptive and computational modeling approach. BMC Neurol 11:53, 2011

21. 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:30, http://www.biomedical-engineering-online.com/content/5/1/30, 2006

22. Oerlemans HM, Perez RS, Oostendorp RA, Goris RJA: Objective and subjective assessments of temperature differences between the hands in reflex sympathetic dystrophy. Clin Rehabil 13:430-438, 1999

23. Schilder JC, van Dijk JG, Dressler D, Koelman JH, Marinus J, van Hilten JJ: Responsiveness to botulinum toxin type A in muscles of complex regional pain syndrome patients with tonic dystonia. J Neural Transm 121:761-767, 2014

24. Sherman RA, Karstetter KW, Damiano M, Evans CB: Stability of temperature asymmetries in reflex sympathetic dystrophy over time and changes in pain. Clin J Pain 10:71-77, 1994

25. Van Marken Lichtenbelt WD, Daanen HAM, Wouters L, Fronczek R, Raymann RJEM, Severens NMW, Van Someren EJW: Evaluation of wireless determination of skin temperature using iButtons. Physiol Behav 88: 489-497, 2006

26. Van Someren EJW, Raymann RJEM, Scherder EJA, Daanen HAM, Swaab DF: Circadian and age-related modulation of thermoreception and temperature regulation: Mechanisms and functional implications. Ageing Res Rev 1:721-778, 2002

27. Wakisaka S, Kajander KC, Bennett GJ: Abnormal skin temperature and abnormal sympathetic vasomotor innervation in an experimental painful peripheral neuropathy. Pain 46:299-313, 1991

28. Wasner G: Vasomotor disturbances in complex regional pain syndrome—A review. Pain Med 11: 1267-1273, 2010

29. Wasner G, Schattschneider J, Baron R: Skin temperature side differences—A diagnostic tool for CRPS? Pain 98:19-26, 2002

30. Wasner G, Schattschneider J, Heckmann K, Maier C, Baron R: Vascular abnormalities in reflex sympathetic dystrophy (CRPS I): Mechanisms and diagnostic value. Brain 124:587-599, 2001