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Multicenter study on the asymmetry of skin temperature in complex regional pain syndrome

An examination of temperature distribution and symptom duration

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Abstract

According to the International Association for the Study of Pain (IASP) and American Medical Association (AMA), the diagnostic criteria for complex regional pain syndrome (CRPS) require the presence of skin temperature asymmetry. In CRPS, it is generally accepted that the temperature of skin of affected limbs changes from warm to cold; however, in our clinical practice, we have experienced many cases with different thermographic characteristics. Therefore, we conducted a retrospective multicenter study that examined the distribution of skin temperature in patients with CRPS and skin temperature asymmetry versus symptom duration.

Patients diagnosed with type 1 or 2 CRPS were recruited. After confirming CRPS according to the IASP diagnostic criteria, infrared thermographic images were evaluated for skin temperature differences (ΔT) between the affected and unaffected limbs.

A total of 296 patients with CRPS were included in this study. The median duration of symptoms was 6 months and the mean ± standard deviation of ΔT was –0.72 ± 1.65°C. A skin temperature difference between bilateral limbs ($|\Delta T|$) of 1°C or less was seen in 131 patients (44.3%); thus, these 131 patients did not meet the IASP criteria for CRPS. Further, cool skin temperature was not observed in 88 patients (29.7%), meaning that these patients did not meet the AMA criteria for CRPS. There was no correlation between the symptom duration and ΔT (Spearman's rho = –0.075, $P = 0.196$) and there was no significant difference in the average ΔT among the 4 symptom duration groups (0–3 months, 4–6 months, 7–12 months, >12 months, $P = 0.08$).

In conclusion, a considerable proportion of the patients that participated in this study did not meet the thermal criteria set forth by the IASP and AMA. Further, there was no correlation between symptom duration and skin temperature difference.

Abbreviations: ΔT = Skin temperature difference between the affected and unaffected side, AMA = American Medical Association, CRPS = complex regional pain syndrome, IASP = International Association for the Study of Pain, IRT = infrared thermography, ODCP = objective diagnostic criteria points.

Keywords: body temperature, complex regional pain syndrome, skin temperature, thermography

1. Introduction

The complex regional pain syndrome (CRPS) is a chronic pain disorder that may develop as a consequence of trauma to the limbs.[1,2]The clinical manifestations of this syndrome are characterized by sensory, vasomotor, sudomotor, or motor/trophic abnormalities.[3] However, the exact pathophysiological mechanism for CRPS has not been established. Further, diagnosis of CRPS is often difficult because confirmation of the syndrome is based on clinical symptoms and signs. Consequently, many criteria have been proposed for the diagnosis or classification of CRPS.[4–7] The International Association for the Study of Pain (IASP) created the name and diagnostic criteria for the syndrome in 1994[6] and, since then, numerous efforts have been made to develop more accurate and valid diagnostic standards. This includes the latest criteria proposed at an expert meeting held in Budapest in 2003.[5] According to the modified clinical diagnostic criteria proposed at this meeting, at least 1 symptom in all 4 symptom categories and at least 1 sign in 2 or more sign categories must be met for a CRPS diagnosis for research purposes. Additionally, at least 1 symptom in 3 out of 4 categories and at least 1 sign in 2 or more sign categories must be met for a CRPS diagnosis in clinical use.[5]

An accurate diagnosis of CRPS is difficult because evaluation of the impairment in a patient with CRPS should be supported by objective findings. To meet this requirement, the Objective Diagnostic Criteria Points (ODCP) for CRPS was proposed by the American Medical Association (AMA). Clinically, a skin temperature difference between the affected and unaffected side has been suggested as an important finding in CRPS. Indeed, both the Budapest criteria and ODCP of the AMA consider differences in skin temperature as an important finding in the diagnosis of CRPS. According to the Budapest criteria, regardless of whether the change in temperature is to cool down or warm up, the temperature difference between the affected and unaffected limbs

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must be more than 1°C to be considered significant.[5] In contrast, the ODCP considers "cool" skin temperature (relative to the unaffected side) as a significant finding and does not rely on a specific degree of temperature change.[8]

Another factor to consider in patients with CRPS is the change of skin temperature with time. An observational study which investigated this factor in 21 patients with CRPS found that skin temperature of the affected limb started off warmer than the unaffected limb, but became cooler as time progressed.[9] However, in this study, the patient follow-up period was variable, ranging from 14 to 127 weeks. In our clinical experience, we have noticed many patients with CRPS whose skin temperature in the affected limb is cold, even in the early stages of the disease. Additionally, we have noted cases where skin temperature asymmetry between the bilateral limbs was not so apparent, or was less than 1°C. These findings do not correspond with the previously mentioned study.[5,8,9]

Thus, the purpose of this study was to evaluate (1) the distribution of the temperature difference between affected and unaffected limbs (ΔT) in patients with CRPS, as well as the proportion of patients who meet the temperature criteria of the IASP and AMA, (2) whether a correlation exists between temperature asymmetry and symptom duration in patients with CRPS, and (3) whether ΔT is different among groups of patients with various disease durations.

2. Materials and methods

2.1. Patients

This retrospective study was approved by our Institutional Review Board (IRB No: B-1008–109–108), and the need for written consent of the patient was waived.

Inclusion criteria were as follows: all patients who visited one of the pain centers from January 2007 to December 2009 due to chronic pain in their extremities and who were diagnosed with CRPS type 1 or 2 based on the criteria of Harden et al[5] (Budapest criteria). A patient with at least 1 symptom in all 4 symptom categories (sensory, vasomotor, sudomotor/edema, and motor/trophic) and at least 1 sign in 2 or more sign categories met the diagnostic criteria for CRPS.

Exclusion criteria were as follows: (1) patients with bilateral pain in their extremities, (2) who had received a sympathetic block or epidural injection within 1 month of the temperature measurement, (3) who had received sympathetic destruction with chemical or radiofrequency, (4) who were taking vasodilating agents, or (5) who had additional concomitant diseases that could contribute to neuropathic pain (e.g., postherpetic neuralgia and diabetic polyneuropathy).

2.2. Skin temperature measurements

Skin temperature was measured using infrared thermography (IRT) images, which were captured following a standard protocol.[10,11] Briefly, patients were acclimated in an isolated room at a mean temperature of 23°C and a relative humidity of 50% for 20 minutes without clothing. IRT images were taken using an IRIS–5000 instrument (Medicore Co., Seoul, Korea), which consisted of a computer-assisted infrared camera and a display module. The device detected infrared energy emitted from the surface of the body, and consisted of a 2-dimensional array with 256×240 (61,440) detectors; temperatures within the range of 17–40°C were measured with an active detector temperature of 77 K. The display module visualized thermal differences as 256 color levels, with a resolution of 0.1°C using 0.9×0.9 mm sized 240×250 pixels. The distance between the camera and the patient was adjusted to 1 m. IRT images were taken of the front, back, and sides of patients in the standing position. When necessary, IRT images of the plantar surface of a patient's hand or feet were also taken.

Resting skin temperature differences in the most painful areas of the affected limb and contralateral side were obtained using the following formula:

ΔT = skin temperature on the affected side – skin temperature on the unaffected side

In accordance with a previous study, several ΔTs were obtained for each patient, and the ΔT exhibiting the maximum absolute value ($|\Delta T|$) was selected as a representative value of their skin temperature abnormality.[11] An example of the IRT images is illustrated in Fig. 1.

2.3. Statistical analysis

Analyses were processed using the IBM SPSS for Windows version 23 statistical package (IBM Inc., Chicago, IL). The distribution of ΔT was plotted in a histogram whereby the proportion of patients who met the temperature criteria of the IASP (> 1°C) and AMA (cool limb) was calculated and depicted. The Kolmorogov–Smirnov test was used to check the normal distribution of the data, and Spearman's rank correlation between ΔT and symptom duration was analyzed. To investigate the mean ΔT difference among the 4 symptom duration groups (0–3 months, 4–6 months, 7–12 months, and >12 months), a 1-way analysis of variance was performed. P values < 0.05 were considered statistically significant. Data are presented as the mean ± standard deviation or median with range.

3. Results

Of the 315 patients who were diagnosed with CRPS at the pain centers of the 3 university hospitals, 296 patients were eligible for this study according to the inclusion and exclusion criteria. The characteristics of the patients are presented in Table 1. The median duration of symptoms was 6 months (range 1–180 months) and the mean ΔT between the affected and unaffected limbs was –0.72 ± 1.65°C (Fig. 2).

A skin temperature difference between bilateral limbs of 1°C or less was seen in 131 patients (44.3%); thus, these 131 patients did not meet the IASP criteria for temperature. Further, the number of patients who did not meet the AMA temperature criteria (cool skin temperature) was 88 (29.7%) (Fig. 3).

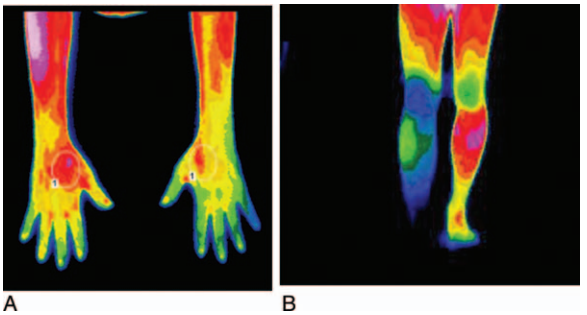

Figure 1. Example of a thermographic image of a patient with CRPS: (A) upper extremities and (B) lower extremities. CRPS = complex regional pain syndrome.

Table 1

Patient characteristics.

Parameter	Data
Sex, M/F	114/79
Age, y, mean ± SD	36.3 ± 14.2
Median symptom duration, mo	7 (range 1–180)
Site, upper extremity/lower extremity	76 / 117
CRPS type, I/II	256 / 40
ΔT, °C, mean ± SD	–0.721 ± 1.65

CRPS = complex regional pain syndrome, SD = standard deviation.

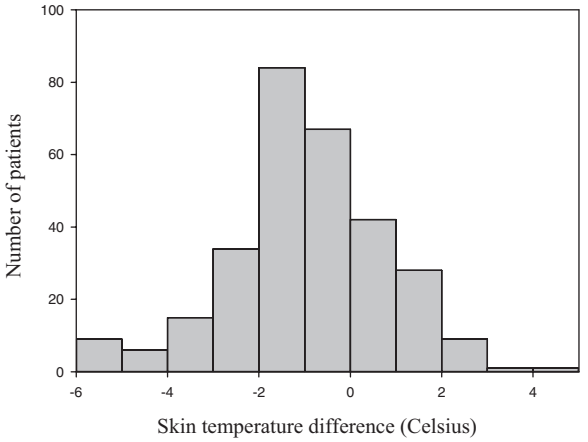

Figure 2. Distribution of ΔT (skin temperature difference between the affected and unaffected limbs). The mean and standard deviation of ΔT was –0.72 ± 1.65°C. ΔT = Skin temperature difference between the affected and unaffected side.

In 60 patients (68.2%), a cooler limb was observed as early as 0–3 months, and a warmer limb was still observed after 12 months in 22 patients (26.8%).

Among the 296 patients included in this study, there was no correlation between symptom durations and ΔT ($P = 0.196$, Spearman's correlation rho = –0.075, Fig. 4), and there was no significant difference in the average ΔT among the 4 symptom duration groups (0–3 months, 4–6 months, 7–12 months, >12 months, $P = 0.08$, Fig. 5).

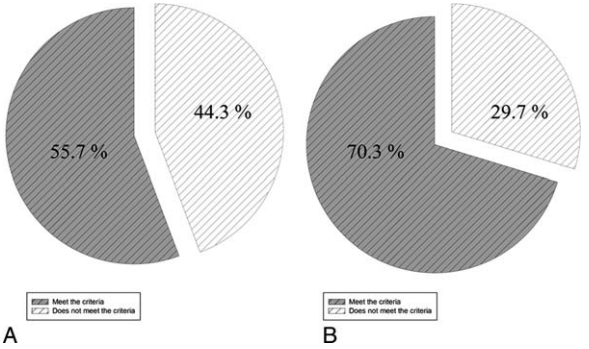

Figure 3. Proportion of patients who did not meet the temperature criteria. (A) 44.3% of the patients did not meet the Budapest criteria and (B) 29.7% of the patients did not meet the American Medical Association criteria.

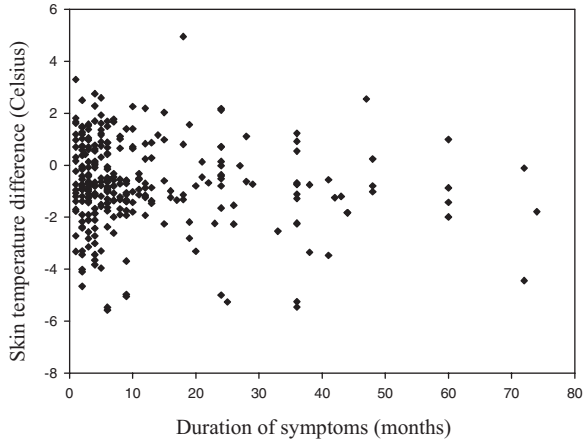

Figure 4. Correlation between ΔT (skin temperature difference between the affected and unaffected limbs) and symptom duration. There was no significant correlation (Spearman's rho = –0.075, $P = 0.196$). ΔT = Skin temperature difference between the affected and unaffected side.

4. Discussion

In this multicenter study, we examined the distribution of skin temperature and the proportion of patients who met the temperature criteria for diagnosis of CRPS according to the IASP and AMA. We also investigated whether there was a correlation between temperature differences and symptom duration in these patients. The epidemiologic data of patients with CRPS in this study were similar to those of previous studies, with the exception that our study population demonstrated male preponderance (female-to-male ratio of 0.7:1) and a younger average age (36.3 ± 14.2 years) than the previously reported population (female-to-male ratio of 2.6–4:1, 43–52 years).[12–14] One possible explanation for this finding could be that obligatory military service in Korea may have increased the risk of trauma and CRPS in young males. Indeed, a previous epidemiologic study of the Korean population[15,16] showed similar characteristics to our study population.

Out study results showed that many patients with CRPS did not meet the temperature criteria previously proposed by the

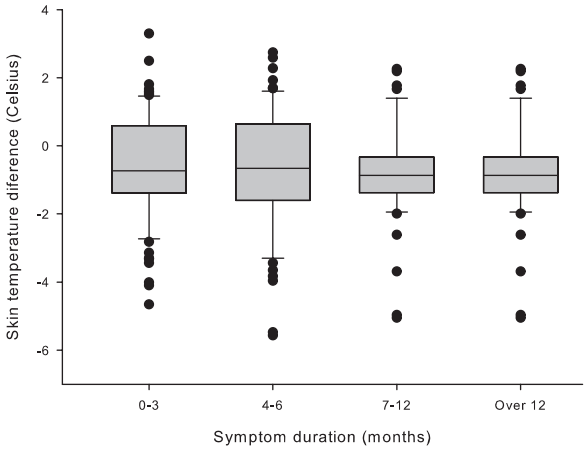

Figure 5. Average ΔT (skin temperature difference between the affected and unaffected limbs) of each symptom duration group. There was no significant difference among the 4 groups ($P = 0.08$). ΔT = Skin temperature difference between the affected and unaffected side.

IASP and AMA and that there was no correlation between skin temperature and symptom duration. Moreover, the average ΔT in the group with varying symptom durations did not significantly differ. These findings suggest that skin temperature does not always change from high to low over time. Consistent with the findings of our current study, Veldman et al[7] conducted a large prospective study of 829 patients and reported several patients with early-stage CRPS with cold limbs and many late-stage patients with warm limbs; however, it should be noted that their study used arbitrary criteria for CRPS diagnosis.

In our study, we employed IRT to measure skin temperature asymmetry in patients with CRPS. Thermography, which detects infrared light emitted by the body, allowed us to visualize changes in body heat and differences in skin temperature between sides. In terms of efficacy in detecting CRPS, IRT is known to have high sensitivity and specificity compared to 3 phase bone scan and magnetic resonance imaging technologies.[17,18] Moreover, there is high inter-examiner reliability when using IRT to evaluate skin temperature abnormalities in patients with CRPS when a region of interest is determined based on patient history and symptoms.[11]

There has been controversy as to whether asymmetries in skin temperature can be used to differentiate between patients with and without CRPS. For example, Bruehl et al[4] studied patients with CRPS and reported that temperature asymmetry accurately discriminated patients with CRPS from those without the syndrome, with the greatest temperature differences obtained at baseline. However, this study was limited to a small number of patients (n = 21). In contrast, Wasner et al[19] studied 25 patients with CRPS and reported a minor difference in skin temperature between both limbs, suggesting that asymmetry in baseline temperatures have a limited value for CRPS diagnosis. The inconsistency in these results may be due to the differences in study methodology and sample size. Our current study examining skin temperature asymmetry in patients with CRPS was one of the largest studies conducted and revealed an overall distribution of skin temperature asymmetry.

Controlled thermography using cold stress or thermal suits has proven useful for CRPS diagnosis.[20] However, there are no validated or standardized methods for applying cold stress before skin temperature measurements. Further, the proposed criteria for CRPS diagnosis does not require the measurement of skin temperature using a cold stressor or thermal suit, and repeated skin temperature measurements are also not required. In clinical practice, skin temperature asymmetry is generally evaluated with digital thermography or through the use of palpation. Stress thermography appears to be a more sensitive and specific method for diagnosing CRPS; however, its methodology should be more standardized and future studies should be conducted to address appropriate diagnostic criteria.[21]

While the exact pathophysiology of CRPS is unknown, there is some agreement that CRPS may be caused by abnormal sympathetic nervous activity. It has been postulated that blood flow abnormalities related to the pathologic dermatome are due to peripheral impairments of sympathetic innervation and hypersensitivity. In a chronic nerve constriction injury model in rats, peripheral vasculature seems to be hypersensitized to circulating catecholamines, which is probably due to an upregulation of adrenoceptors, leading to cutaneous vasoconstriction.[22,23] Moreover, warm, affected extremities in patients with CRPS can be explained by a functional inhibition of sympathetic vasoconstrictor activity in the skin, leading to cutaneous vasodilation.[24] Studies which have shown a reduction in norepinephrine levels of the affected extremity from the venous effluent areas support this idea.[25,26]Further, some studies have suggested a relationship between increased inflammatory responses and CRPS; thus, anti-inflammatory treatments could be effective target-specific clinical approaches to CRPS.[27,28] As the degree of sympathetic denervation or inflammatory reaction may vary depending on the underlying pathophysiological condition, the degree of skin temperature asymmetry may show a normal distribution. Therefore, thermographic skin temperature differences may be better used in screening for CRPS rather than in evaluating the presence of permanent impairment.

In our study, we classified disease duration into 4 groups (0–3 months, 4–6 months, 7–12 months, and >12 months). Because there are no definable timetables for CRPS stages, we followed the Veldman study[7] with some modification. Veldman's study was the largest prospective observation study on the signs and symptoms of CRPS, in which he classified CRPS disease duration into 4 categories ($0-2$, $2-6$, $6-12$, >12 months). In that classification, the 2nd and 6th months are duplicated within 2 of the 4 categories, which can be confusing. Another review article on CRPS indicated that the early stage of the syndrome occurs within $0-3$ month.[29,30] Together, we used the guidelines from these 2 studies as the basis for our classification of symptom duration.

There were some limitations to this study that should be addressed. First, our data were cross-sectional in nature and were only gathered 1 time from each patient. Although a prospective measurement of skin temperature with subsequent follow-up measures may yield more meaningful data, evaluations of skin temperature over the course of the disease may be difficult because interventional treatments for patients with CRPS can easily cause changes in skin temperature. Despite this limitation, our report remains one of the largest thermographic studies on patients with CRPS. Second, the patients included in this study were regionally and racially limited. Specifically, we only enrolled Korean patients; therefore, the caution should be made in generalizing our results. Third, the assessors involved in this study were not blinded to patient symptoms. However, knowledge of a patient's symptomatic site is crucial in measuring skin temperature[11]; thus, the assessor could not be blinded in this study.

In conclusion, a large proportion of the patients that participated in this study did not meet the thermal criteria set forth by the IASP and AMA and we did not observe a correlation between the duration of symptoms and skin temperature differences in patients with CRPS. Therefore, the absolute difference in skin temperature between the bilateral limbs of patients with CRPS did not appear to be useful as a diagnostic criterion for the disease. Further, our results suggest that this value may not be appropriate to use to evaluate permanent impairment in patients with CRPS. Thus, future studies addressing the suitability of such criteria in evaluating CRPS-induced damage are required.

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