

Diagnosing Sensory Abnormalities with Either Normal Values or Values from Contralateral Skin

Comparison of Two Approaches in Complex Regional Pain Syndrome I

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Background: To diagnose sensory abnormalities, patient values can be compared with values of the general population (absolute approach) or to values measured at contralateral homologous skin (relative approach). The current study gives normal values for both approaches and compares the advantages of each method by applying the technique to patients with complex regional pain syndrome type I (CRPS I).

Methods: In 50 healthy control subjects, sensory and pain thresholds were measured for pressure, warmth, and cold on both wrists and both feet. In 53 patients with unilateral CRPS I (33 hand, 20 foot), the same assessments were conducted twice, at an interval of 1 month.

Results: In control subjects, contralateral homologous sides have approximately the same sensitivity, supporting the validity of the relative approach in patients. Hypoesthesia and allodynia can be diagnosed by either the absolute or relative approach, whereas hyperesthesia and hypoalgesia can only be identified with the relative approach. The two approaches obtain different results in 20% of cases. Age, gender, and subject criteria may influence the absolute but not the relative approach. Both approaches are comparable with regard to reproducibility. Frequency distributions of sensory abnormalities in chronic CRPS

I are presented. The most frequent diagnoses were cold allodynia and mechanical hypoesthesia and allodynia.

Conclusions: To divide sensory characteristics into a binary classification of "normal" and "abnormal," the relative approach is the best choice, with the exception of cases in which the contralateral homologous side is absent or affected by disease. The authors recommend the relative approach for both research and clinical purposes. (Key words: Method of levels; method of limits; quantitative thermal testing.)

SENSORY characteristics are important in confirming the diagnosis of many diseases. The subjective phenomena of sensory function are objectively evaluated by quantitative sensory analysis. Results of sensory tests are usually presented quantitatively (*i.e.*, in degrees Centigrade or in grams pressure). For clinical purposes, however, it is also useful to present results in a binary classification of "normal" or "abnormal."

To diagnose a sensory abnormality a point of reference, *i.e.*, a normal value, is necessary. There are two obvious approaches to trace this point of reference. First, the mean normal value could be obtained from a large sample of healthy subjects who are tested on the same location, during the same circumstances, while applying the same technique. In this approach, measured values that differ more than 2 SDs from the mean normal values are considered abnormal.¹⁻³ We refer to this as the absolute approach. Second, the normal value could be obtained from a contralateral homologous location within the same subject, tested during the same circumstances, while applying the same technique. This approach is based on the hypothesis that during normal conditions, corresponding areas on opposite sides of the body have approximately the same sensitivity. Because no SD is known using this approach, the cutoff point between normal and abnormal is usually assigned arbitrarily.⁴ We refer to this as the relative approach and present empirically obtained cutoff points.

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There are advantages to each method. The absolute approach is more efficient, requiring measurements only in the affected regions, and can be applied to any location, including midline locations that have no contralateral control region. The relative approach is relatively immune to sources of bias, such as age, gender, and presence of pain, that influence the absolute approach. The relative approach is also not restricted to testing at standard sites for which control values have been established.

Patients with Complex Regional Pain Syndrome type I (CRPS I) almost invariably have symptoms of sensory abnormalities within pathologic zones of skin.⁵ The incidence, type, and extent of these abnormalities vary considerably across these patients, so that no single type of abnormality or its extent can be used as an inclusion criterion to diagnose CRPS I.⁶ Nevertheless, confirmation of the presence of one or more sensory abnormalities by quantitative sensory analysis may serve as an important adjunctive aid in confirming the diagnosis of CRPS I. Sensory testing may also be helpful in characterizing pathophysiological pain mechanisms and matching such mechanisms to appropriate therapies.

The current study evaluated and compared absolute and relative approaches. We measured sensory and pain thresholds for pressure, cold, and warmth on both wrists or both feet of healthy control subjects, determining mean thresholds and mean left-right differences. Using similar methods, we performed two successive tests on CRPS I patients with one affected hand or foot. The aims of the current study were as follows: (1) to assess whether corresponding areas on opposite sides of the body have approximately the same sensitivity in normal subjects, and thus whether the relative approach is acceptable; (2) to provide a database sufficient for the determination of sensory abnormalities to warmth, cold, and pressure using either the relative or absolute approach; (3) to determine whether the absolute and relative approach measure the same phenomenon; (4) to assess the influence of factors such as age and gender on each approach; (5) to ascertain the reproducibility of the absolute and the relative approach; and (6) to describe the frequency distribution of sensory abnormalities to warmth, cold, and pressure in randomly selected CRPS I patients.

Subjects and Methods

Patients

Fifty-three patients with CRPS I (37 women and 16 men), with a mean age of 38.6 yr (range, 21–65 yr) were

studied; 33 patients had CRPS I of an arm, whereas 20 had CRPS I of a leg. The mean duration of CRPS I was 38.2 months (range, 9–120 months). The CRPS I was precipitated by trauma in 25 patients, by surgery in 24 patients, and had started spontaneously in the last 4 patients. All patients fulfilled the diagnostic criteria for CRPS I of the International Association for the Study of Pain, which include the criterion that the initiating noxious event is not associated with significant nerve injury.⁷ Clinically, the CRPS I was restricted to one extremity with an extent that included the whole hand or the whole foot. Patients with any signs of CRPS I beyond the affected extremity were excluded. All patients had severe pain (*i.e.*, at least 5 cm on a 10-cm visual analog scale) that was unresponsive to conventional treatments, and all patients were functionally impaired. Discoloration of the skin (red or blue) was present in 48 patients, chronic edema was present in 44 patients, and hyperhidrosis was present in 40 patients. In the affected area, 31 patients noted a changed growth of nails, and 11 patients noted a changed growth of hair.

Detection and pain thresholds for pressure, warmth, and cold were assessed twice, at an interval of 1 month. During this month the patients did not receive any treatment.

Normal Subjects

For each sensory modality, 50 subjects (25 men and 25 women) were tested in both upper extremities and 50 (25 men and 25 women) in both lower extremities. The volunteers had no known neurologic deficit; no history of pain, impairment, or surgery in the tested limbs; no known systemic disease; and no use of sedative medication. Each time, the 50 volunteers were equally divided over the following five age groups: 20–30 yr, 31–40 yr, 41–50 yr, 51–60 yr, and 61–70 yr. Thus, each age group consisted of five male and five female subjects.

Informed consent was obtained from all patients and control subjects according to the Declaration of Helsinki. The study protocol was approved by the Ethical Committee of Maastricht University Hospital, where the research took place.

Definitions

The definitions of pain terms used in the current study have been stated as follows by the International Association for the Study of Pain⁷:

Hypoesthesia: decreased sensitivity to stimulation (raised detection threshold)

Hyperesthesia: increased sensitivity to stimulation (lowered detection threshold)

Allodynia: pain caused by a stimulus that does not normally provoke pain (lowered pain threshold)

Hypoalgesia: diminished pain in response to a normally painful stimulus (raised pain threshold)

Hyperalgesia: an increased response to a stimulus that is normally painful (increased pain on suprathreshold stimulation)

Whereas the other sensory abnormalities can be measured by changing the intensity of a stimulus, hyperalgesia must be assessed while applying a constant painful stimulus. Therefore, mean values and SDs cannot be expressed in physical units such as degrees Centigrade, but have to be expressed in units of subjective response intensity. Given the numerous methods for measuring pain intensity, and issues of response bias, we chose to confine our measurements to physical units of stimulus intensity.

Mechanical Sensibility

The Semmes-Weinstein Pressure Aesthesiometer (Smith & Nephew Rolyan Inc., Germantown, WI) was used to measure detection and pain thresholds for pressure. The instrument includes a kit of 20 probes, each consisting of a nylon monofilament attached to a rod. Each probe is marked with a number ranging from 1.65 to 6.65 that represents the logarithm of the force in tenths of milligrams necessary to bend the monofilament.⁸

Ascending levels of filament forces were applied up to the pressure detection threshold, a level that the subject detects in at least two of three trials. The pressure pain threshold, the minimum force at which the subject reports pain, was determined in a similar manner. To evaluate all nerves supplying the hand or foot, we defined nine stimulation sites representative of various peripheral nerves and dermatomes (fig. 1). From the nine thresholds obtained for detection and pain, the mean detection and pain thresholds for the hand or foot were calculated in grams. During testing, subjects kept their eyes closed and were thus unable to observe their hands, feet, or the probes.

Warmth and Cold Sensibility

Thresholds for warmth, cold, heat-induced pain, and cold-induced pain were measured using a 5 × 2.5-cm water-cooled Peltier probe (TSA2001; Medoc Ltd., Ramat Yishai, Israel). The probe was applied at a standard baseline temperature of 32°C. The high temperature limit was set at 50°C and the low at 0°C. When these

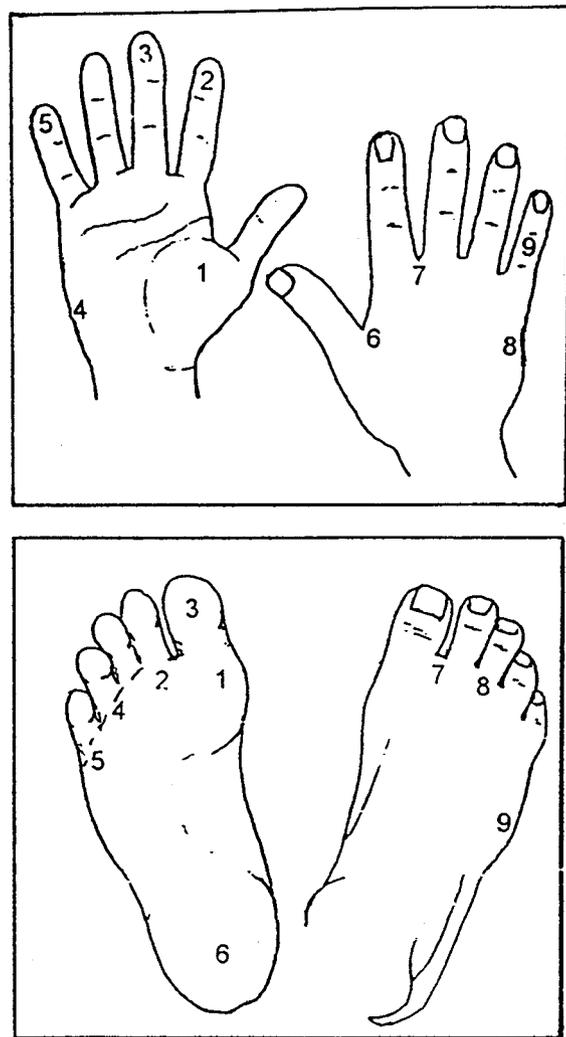


Fig. 1. Sites at the hand and foot where pressure sensibility was tested. Hand sites are innervated by the median nerve (sites 1–3), the ulnar nerve (sites 4, 5, 8, and 9), and the radial nerve (sites 6 and 7). Foot sites are supplied by the medial plantar nerve (sites 1–3), the lateral plantar nerve (sites 4–6), the deep peroneal nerve (site 7), the superficial peroneal nerve (site 8), and the sural nerve (site 9).

temperatures were reached, stimulus temperature returned to baseline.

Warmth and cold detection thresholds were assessed using the Method of Levels.³ The final result is the mean of two measures. Warmth and cold pain thresholds were assessed with the Method of Limits.³ Thresholds for the foot were assessed at the dorsal aspects of both feet, immediately proximal to the basis of the second and third toe. Thresholds for the hand were assessed at the volar aspects of both wrists, immediately proximal to the

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base of the hand. The thermode was attached to the skin by means of an elastic Velcro tape. Care was taken to minimize variation of thermode application pressure.

Calculation Procedures

Absolute Approach (vs. Reference Values). Measurements of the left and right side of normal subjects were analyzed separately. For all sensory modalities, linear regression analysis was performed using age and gender as independent variables. When this revealed a statistically significant influence of gender, the groups of men and women were analyzed separately. When no influence of gender was found for either left or right sides, the regression analysis was repeated using only age as the independent variable. When this analysis revealed no influence of age, data were presented as mean \pm 2 SD for the complete group. Results from both sides were combined if paired *t* tests did not show differences between both sides and if regression coefficients for age—if applicable—were of comparable size. Mean values and SDs were calculated from these combined numbers. In cases in which both mean threshold and variance increased with age (cold and warmth detection thresholds at the foot), mean values were calculated for the five age groups separately, and the regression line through these five values was used to compute the normative value. No subject reported pain during pressure testing, even when the largest filament was applied. Consequently, mechanical hypoalgesia cannot be identified using monofilaments; mechanical allodynia was defined as pain produced by any of the filaments.

After calculating mean values and SDs, we classified the results from the CRPS I patients' affected extremity as normal or abnormal. This classification was not always possible because the combination of the mean result and the SDs could exceed the thermal 32°C baseline, or the limits of the thermal test at 0°C and 50°C, and the limits of the pressure test at 0.0045 g and 447 g for specific conditions. Thus, although hypoesthesia and allodynia could be identified, we were unable to assess hyperesthesia and hypoalgesia with this method.

Relative Approach (vs. Unaffected Contralateral Homologous Skin). In controls, the mean left-to-right difference (threshold left side minus threshold right side) was calculated for all sensory modalities. As shown by linear regression analysis, the mean difference was not influenced by age and gender for any sensory modality. For all sensory modalities on hands and feet, the limits of normality were calculated as mean difference \pm 2 SD (reference boundaries). Because no subject reported pres-

sure pain at the maximal filament size (447 g), we defined any difference below zero as mechanical allodynia (*i.e.*, any pain to monofilament stimulation in the affected region). In CRPS I patients, the difference between affected and unaffected sides were calculated (threshold affected side minus threshold unaffected side).

Statistics

As previously mentioned, linear regression analyses were applied to assess the influences of age and gender on sensory thresholds.^{9,10} To satisfy requirements of independence, regression analyses for the absolute approach were performed separately for the left and right side. Values for the left and right side were pooled in the computation of reference boundaries (mean \pm 2 SD) because independent observations are not necessary for mean values and SDs. The Fisher exact test was used to compare the frequency of diagnoses in hands and feet. McNemar's test was applied to compare the frequency of diagnoses by either the absolute or the relative approach. The coefficient of repeatability (CR) is a measure of the actual range of variability within subjects and indicates that there can be 95% confidence that results of two determinations made on the same subject during the same circumstances would differ by less than CR.¹¹ Calculation of CR was as follows: the differences between the two measurements were squared, added together, and divided by *n*; the square root was then calculated to obtain the SD of the differences. The CR is twice this figure (CR = 2 SDs of the differences). κ Values were calculated to assess the reproducibility of two successive measurements of either the absolute approach or the relative approach. Two-tailed *P* values < 0.05 indicate statistical significance.

Results

Table 1 presents mean values with prediction intervals for detection and pain thresholds of both hands or both feet of control subjects and CRPS I patients with one affected extremity. The warmth and cold detection thresholds from the unaffected side of CRPS I patients did not differ significantly from control values. However, the pressure detection threshold was higher on the unaffected CRPS I side. Control values for warmth and cold pain thresholds were more extreme than unaffected-side CRPS I values. The differences between results obtained from controls and from the unaffected side of patients may be considered the result of response bias. Because

Table 1. Detection and Pain Thresholds for Contralateral Extremities of Control Subjects and CRPS Patients with One Affected Limb

| | Control Subjects | | CRPS Patients | |
|--------|-------------------|-------------------|-------------------|------------------|
| | Left Side | Right Side | Unaffected Side | Affected Side |
| Wrist* | | | | |
| PDT | 0.08 (0.01/0.14) | 0.07 (0.00/0.15) | 0.14 (-0.04/0.32) | 7.9 (-79.7/94.4) |
| WDT | 32.6 (31.7/33.6) | 32.5 (31.7/33.3) | 32.7 (31.7/33.7) | 33.1 (31.2/35.1) |
| CDT | 31.3 (30.9/31.8) | 31.3 (30.9/31.7) | 31.3 (30.7/31.9) | 30.9 (29.5/32.3) |
| PPT | — | — | — | 113 (-231/457) |
| WPT | 46.3 (42.5/50.2) | 46.5 (42.7/50.3) | 44.6 (38.9/50.4) | 40.3 (32.0/48.5) |
| CPT | 5.2 (-2.7/13.1) | 5.4 (-2.3/13.1) | 10.6 (-2.4/23.7) | 21.0 (5.2/36.9) |
| Foot† | | | | |
| PDT | 0.36 (-0.20/0.92) | 0.34 (-0.10/0.77) | 0.98 (-0.72/2.67) | 4.5 (-10.4/19.3) |
| WDT | 35.6 (29.7/41.4) | 35.4 (29.8/41.0) | 35.7 (28.1/43.3) | 36.5 (28.1/44.8) |
| CDT | 30.9 (29.1/32.7) | 30.9 (29.5/32.3) | 30.0 (24.2/35.8) | 28.8 (19.3/38.4) |
| PPT | — | — | — | 137 (-184/458) |
| WPT | 46.8 (43.1/50.4) | 46.7 (43.2/50.1) | 44.1 (38.7/49.4) | 41.6 (33.1/50.1) |
| CPT | 3.6 (-4.1/11.4) | 3.4 (-4.1/11.0) | 10.5 (-6.6/27.7) | 20.1 (-1.4/41.7) |

Mean detection and pain thresholds, with 95% prediction intervals at wrists and feet of 50 healthy volunteers and 53 patients with CRPS of the wrist (n = 33) or foot (n = 20). Temperature thresholds are expressed in degrees centigrade (baseline temperature = 32°C); pressure thresholds are expressed in grams force. For unaffected locations, pressure pain thresholds are immeasurable using Semmes-Weinstein monofilaments because the thickest filament is not painful to healthy subjects.

* n = 50 for control subjects; n = 33 for complex regional pain syndrome (CRPS) patients.

† n = 50 for control subjects; n = 20 for CRPS patients.

PDT = pressure detection threshold; WDT = warmth detection threshold; CDT = cold detection threshold; PPT = pressure pain threshold; WPT = warmth pain threshold; CPT = cold pain threshold.

the type of sensory abnormalities varies between CRPS I patients (see below), the mean values of the affected side from table 1 do not provide a clinical image of the average CRPS I patient.

Normative Values

Table 2 presents the mean detection and pain thresholds with reference boundaries at the wrist and foot for the 50 healthy individuals. For detection thresholds, a

score more extreme than the reference boundary indicates hypoesthesia. A pain threshold more extreme than the reference boundary indicates allodynia. In cases in which the reference boundary is age- or gender-dependent, it can be calculated for the individual patient by multiplying the age of the patient with the value from table 2. Thus, the reference boundary for pressure detection at the foot of a 20-yr-old female subject is 0.31 g ($0.12 + 0.0097 \times 20$), whereas for an 80-yr-old man it is

Table 2. Mean Detection and Pain Thresholds, with Reference Boundaries at Wrists and Feet

| | Wrist | | Foot | |
|-----|-------------------------|--|------------------------|--|
| | Mean | Reference Bound | Mean | Reference Bound |
| WDT | 32.6 | 33.5 | Female 34.6 Male AD | 38.7 $31.0 + 0.24 \times \text{age}$ |
| CDT | 31.3 | 30.9 | AD | $32.9 - 0.073 \times \text{age}$ |
| WPT | 46.4 | 42.6 | 46.7 | 43.2 |
| CPT | AD | $5.99 + 0.14 \times \text{age}$ | 3.5 | 11.2 |
| PDT | Female 0.066 Male AD | 0.12 $0.09 + 0.00068 \times \text{age}$ | Female AD Male AD | $0.12 + 0.0097 \times \text{age}$ $0.51 + 0.0093 \times \text{age}$ |

Mean detection and pain thresholds, with reference boundaries (mean \pm 2 SD) at wrists and feet of 50 healthy volunteers (25 male, 25 female). Temperature thresholds are expressed in degrees centigrade (baseline temperature = 32°C); pressure thresholds are expressed in grams force. The reference boundaries are unidirectional because the boundaries in the other direction are beyond baseline or extreme values of measurement. Pressure pain thresholds are immeasurable using Semmes-Weinstein monofilaments because the thickest filament is not painful to healthy subjects.

WDT = warmth detection threshold; AD = age dependent; CDT = cold detection threshold; WPT = warmth pain threshold; CPT = cold pain threshold; PDT = pressure detection threshold.

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Table 3. Mean Left–Right Differences, with Upper and Lower Reference Bounds at Wrists and Feet

| | Wrist | | | Foot | | |
|-----|--------|----------|----------|-------|----------|----------|
| | Mean | Lower RB | Upper RB | Mean | Lower RB | Upper RB |
| WDT | 0.1 | −0.8 | 1.0 | 0.2 | −3.5 | 3.8 |
| CDT | 0.01 | −0.4 | 0.4 | −0.04 | −1.6 | 1.5 |
| WPT | −0.2 | −2.3 | 1.9 | 0.1 | −1.9 | 2.2 |
| CPT | −0.2 | −4.1 | 3.6 | 0.2 | −2.7 | 3.1 |
| PDT | 0.0015 | −0.054 | 0.057 | 0.026 | −0.17 | 0.22 |

Mean left side minus right side differences of detection and pain thresholds of 50 healthy volunteers (25 male, 25 female) with upper and lower reference boundaries (RB) at wrists and feet. Temperature thresholds are expressed in degrees centigrade (baseline temperature = 32°C); pressure threshold is expressed in grams force. Pressure pain differences are immeasurable using Semmes–Weinstein monofilaments because the thickest filament is not painful to normal subjects.

WDT = warm detection threshold; CDT = cold detection threshold; WPT = warmth pain threshold; CPT = cold pain threshold; PDT = pressure detection threshold.

1.25 g ($0.51 + 0.0093 \times 80$). The reference boundaries to hyperesthesia or hypoalgesia are beyond baseline or extreme values of measurement, *i.e.*, 0, 32, or 50°C for temperature and 0 or 447 g for pressure. Thus, hyperesthesia and hypoalgesia, in principle, cannot be diagnosed by means of the absolute approach.

Mean left–right differences of the 50 healthy controls, with upper and lower reference boundaries, are presented in table 3. All differences were near zero, indicating that contralateral homologous body areas have approximately the same sensitivity in normal subjects. The lower boundaries allow the diagnosis of hyperesthesia and hypoalgesia in addition to hypoesthesia and allodynia. Figures 2 and 3 present normal individuals and patients compared either with the absolute approach or with the relative approach. These figures show the tight grouping of normal values using the relative approach, the use of this approach to identify hyperesthesia and hypoalgesia, and the influence of age on only the absolute approach.

Absolute Approach

Table 4 shows the percentage of CRPS I patients with sensory abnormalities defined by the absolute approach. There were no statistically significant differences between upper and lower extremity patients. Approximately 75% of patients were diagnosed with mechanical and cold allodynia, and mechanical hypoesthesia. More than 50% of the patients experienced warmth allodynia, whereas hypoesthesia to cold (approximately 40%) and warmth (approximately 20%) was found less often. The CRs in table 4 indicate the possible variability between two successive determinations in the same subject. Feet CRs were up to 10-fold as high as hand CRs for mechan-

ical detection and pain and cold detection thresholds. For the other sensory modalities, hand and feet CRs were comparable. κ Values refer to the agreement between two successive measurements. Most values were greater than 0.40, indicating reasonable to good agreement.¹⁰ Reproducibility of warmth modalities appeared to be poor.

Relative Approach

As shown in table 4, more types of sensory abnormalities in CRPS I patients were diagnosed using the relative approach. As with the absolute approach, there were no statistically significant differences between the upper and lower extremities in patients. The frequencies of abnormality measured with the relative approach were similar or lower as compared with the absolute approach frequencies. Only the frequency of mechanical hypoesthesia at the wrist was statistically significantly lower ($P = 0.008$). Sensory abnormalities that could be identified only using the relative approach appeared to be rare in CRPS I patients; mechanical hyperesthesia ($\pm 20\%$) appeared to be the most frequent abnormality. CRs of the relative approach were largely similar to CRs of the absolute approach. Only in the case of the cold pain threshold, the relative approach showed a greater variability (15–20°C *vs.* $\pm 10^\circ\text{C}$), indicating that this threshold also varied on the unaffected side between two determinations. Again, most κ values were greater than 0.40 (reasonable to good agreement¹⁰), although in most cases the relative approach value was lower than the absolute approach value. Because of the low frequency of some sensory abnormalities, several κ values were zero or negative, meaning that the agreement was equal to or below what could be expected on the basis of chance.

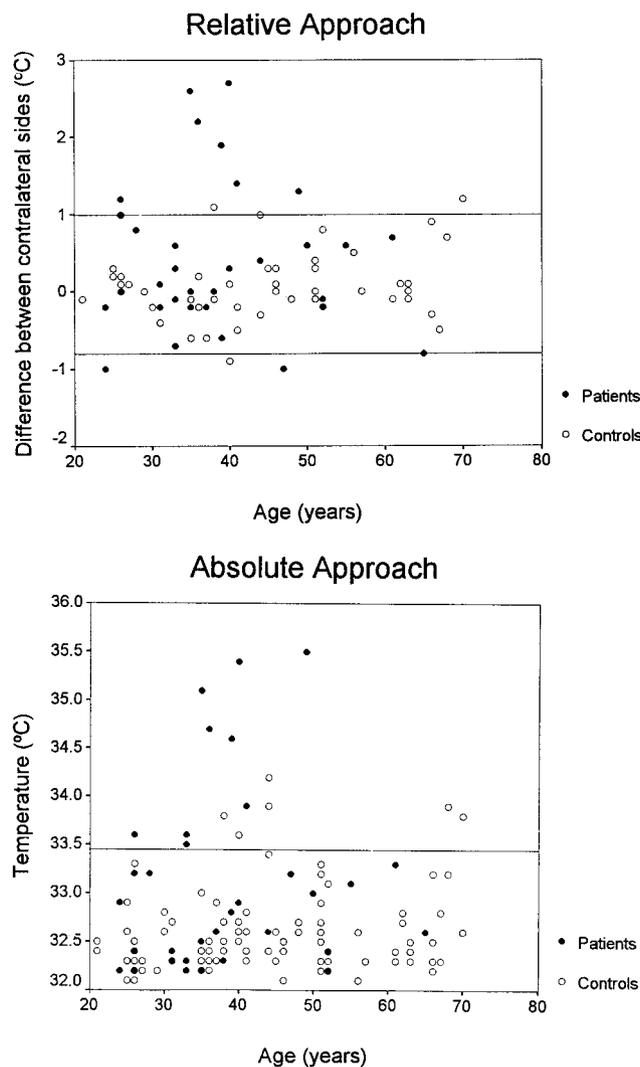


Fig. 2. Comparison of the relative (*top*) and absolute (*bottom*) approach to diagnose abnormalities in warmth detection at the wrist. Open circles represent healthy individuals (threshold left side minus threshold right side), and filled circles represent CRPS I patients (threshold affected side minus threshold unaffected side). Lines refer to mean \pm 2 SD. Note that two patients showed hyperesthesia with the relative approach.

Agreement Absolute and Relative Approach

To determine whether the absolute and relative approach measure the same phenomenon, we compared diagnoses by both methods on the individual subjects determined from detection thresholds for pressure, warmth and cold, and pain thresholds for warmth and cold.

In approximately 80% of cases (range, 68% pressure detection to 89% cold detection), the absolute and relative approach showed the same result (both positive or

negative). In 10% (range, 6% warmth pain to 13% pressure detection), the absolute approach indicated an abnormality while thresholds were normal according to the relative approach. In another 10% (range, 4% cold detection to 19% warmth pain), the relative approach showed an abnormality while the absolute approach did not. For pressure detection, there were actually opposite diagnoses by both methods in 11% of cases. These differences were systematic; in all cases the absolute ap-

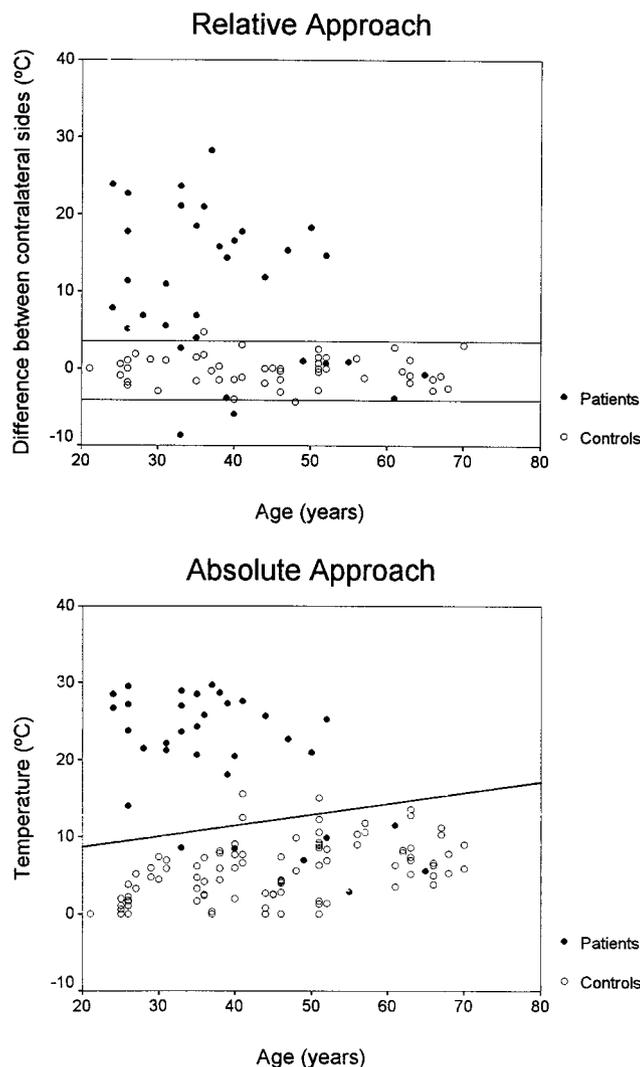


Fig. 3. Comparison of the relative (*top*) and absolute (*bottom*) approach to diagnose abnormalities in cold pain at the wrist. Open circles represent healthy individuals (threshold left side minus threshold right side), and filled circles represent CRPS I patients (threshold affected side minus threshold unaffected side). Lines refer to mean \pm 2 SD. Note that normal values of the absolute approach are age-dependent and that two patients showed hypoalgesia with the relative approach.

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Table 4. Sensory Abnormality Frequencies in CRPS Patients, Detected with Use of the Absolute and Relative Approaches

| | Absolute Approach | | | Relative Approach | | |
|--------------------------|-------------------|--------|----------|-------------------|--------|----------|
| | % Frequency | CR | κ | % Frequency | CR | κ |
| Mechanical hypoesthesia | | | | | | |
| Hands | 73 (24/33) | 1.0 g | 0.57 | 48 (16/33) | 1.0 g | 0.45 |
| Feet | 75 (15/20) | 8.2 g | 0.10 | 55 (11/20) | 7.7 g | 0.51 |
| Mechanical hyperesthesia | | | | | | |
| Hands | — | 1.0 g | — | 15 (5/33) | 1.0 g | 0.24 |
| Feet | — | 8.2 g | — | 25 (5/20) | 7.7 g | 0.39 |
| Mechanical allodynia | | | | | | |
| Hands | 82 (27/33) | 110 g | 1.00 | 82 (27/33) | 110 g | 1.00 |
| Feet | 90 (18/33) | 205 g | 0.62 | 90 (18/20) | 205 g | 0.62 |
| Cold hypoesthesia | | | | | | |
| Hands | 33 (11/33) | 0.7°C | 0.81 | 36 (12/33) | 1.1°C | 0.74 |
| Feet | 40 (8/20) | 10.2°C | 0.71 | 20 (4/20) | 7.8°C | 0.69 |
| Cold hyperesthesia | | | | | | |
| Hands | — | 0.7°C | — | 0 | 1.1°C | 0 |
| Feet | — | 10.2°C | — | 5 (1/20) | 7.8°C | 0 |
| Cold allodynia | | | | | | |
| Hands | 79 (26/33) | 9.7°C | 0.80 | 73 (24/33) | 16.8°C | 0.67 |
| Feet | 75 (15/20) | 10.2°C | 0.63 | 70 (14/20) | 18.6°C | 0.48 |
| Cold hypoalgesia | | | | | | |
| Hands | — | 9.7°C | — | 6 (2/33) | 16.8°C | 0.65 |
| Feet | — | 10.2°C | — | 15 (3/20) | 18.6°C | 0.32 |
| Warmth hypoesthesia | | | | | | |
| Hands | 27 (9/33) | 2.0°C | 0.18 | 24 (8/33) | 2.0°C | -0.40 |
| Feet | 20 (4/20) | 4.0°C | 0.69 | 10 (2/20) | 4.5°C | 0.44 |
| Warmth hyperesthesia | | | | | | |
| Hands | — | 2.0°C | — | 9 (3/33) | 2.0°C | 0.48 |
| Feet | — | 4.0°C | — | 5 (1/20) | 4.5°C | 0 |
| Warmth allodynia | | | | | | |
| Hands | 70 (23/33) | 7.5°C | 0.41 | 73 (24/33) | 6.2°C | 0.29 |
| Feet | 55 (11/20) | 5.1°C | 0.49 | 65 (13/20) | 6.4°C | 0.22 |
| Warmth hypoalgesia | | | | | | |
| Hands | — | 7.5°C | — | 9 (3/33) | 6.2°C | 0.78 |
| Feet | — | 5.1°C | — | 5 (1/20) | 6.4°C | -0.07 |

Frequencies of sensory abnormalities detected in CRPS patients with an affected hand ($n = 33$) or foot ($n = 20$). There can be 95% confidence that results of two determinations made on the same subject in the same circumstances and differs by less than this coefficient. κ Values refer to agreement between two successive measurements.

CRPS = complex regional pain syndrome; CR = coefficient of reproducibility.

proach identified hypoesthesia, while the relative approach identified hyperesthesia.

Discussion

Quantitative sensory analysis evaluates the functional status of primary afferents. Clinically, quantitative sensory analysis can confirm diagnoses and influence the choice of appropriate therapy. In this case, the primary goal of quantitative sensory analysis is to assess whether a disease has changed nerve function. Normally, patients are first evaluated after initiation of the disease and consequently the original nerve function is unknown. In

the absence of a predisease baseline, the clinician must determine a comparison value; there is no normative gold standard. Normal values from other individuals can be used to show an aberrant value but cannot show whether nerve function has changed. Conceptually, this change could be determined by comparison of the affected location with a homologous area on the unaffected side. Finding asymmetry is a basic principle of the clinical neurologic examination.¹² Evaluation of the motor and sensory systems and of reflexes always compares both arms and both legs. Abnormalities in maximum motor nerve conduction velocity and sensory nerve action potentials are also revealed by asymmetry between left and right, even when the values are normal abso-

lutely because these parameters should be the same on both sides.¹³

To the best of our knowledge, the current study is the first to show the validity of the relative approach (comparing left and right) for the diagnosis of sensory abnormalities. The results showed that bilateral homologous areas have approximately similar sensory function in healthy individuals, and thus there is good reason to assume that relative values from contralateral homologous skin in patients are good indicators of original nerve function in affected skin. The study also shows that the absolute and relative approach have similar results in no more than 80% of cases. In 10% of cases, only the absolute approach shows an abnormality, and in the other 10% of cases, solely the relative approach identifies abnormal thresholds. The contrasts between the results of both methods indicate that these methods do not measure an entirely similar phenomenon, and thus results from the absolute or the relative approach cannot be compared.

Two striking differences between the diagnostic criteria of each method were shown. First, normal values of the absolute approach were often found to be influenced by age and gender. These influences are well known and have been described in many studies.^{2,3,14-17} We found no influence of age and gender with the relative approach, which simplifies the evaluation of abnormal sensory function. Second, the absolute approach could not identify instances of hyperesthesia and hypoalgesia, supporting previous findings by Verdugo and Ochoa.¹ Although the frequencies of hyperesthesia and hypoalgesia were low for CRPS I patients, the presence of hyperesthesia and hypoalgesia is an important finding. We consider the fact that the absolute approach to assess sensory abnormalities, by definition, classifies these patients as "normal" as a significant disadvantage.

The relative approach appears to be the best choice, with minor caveats. First, a contralateral homologous side is not always available; in such cases the absolute approach must be used. Second, variation in thresholds of the control side may influence the results. Because the repeatability of the relative approach was approximately similar to that of the absolute approach, the influence of control side variations is likely insignificant. Finally, the disease process may progress to include the contralateral region,¹⁸ resulting in a pathologic control value minimally different from the affected side. Clinicians must be aware of this possibility and be particularly sensitive to complaints about the contralateral region. In the presence of such complaints, normative values from the

absolute approach must be used. The current study showed that patient values measured on a definitely unaffected site may still differ from control values. However, despite the absence of symptoms, the possibility of contralateral involvement can never be ruled out.¹⁹ Unlike patients, control subjects are well motivated and eager to obtain optimal scores: their detection thresholds are lower and pain thresholds are higher (response bias²⁰). This may explain why patients accept less heat and cold than controls, and why control subjects need lower stimuli than patients to detect pressure. The influence of these differences are eliminated or at least minimized by applying the relative approach.

Although different in frequency, all sensory abnormalities (hypoesthesia, hyperesthesia, hypoalgesia, allodynia) were shown in the current study in the affected area of chronic CRPS I patients by heat, cold, and pressure stimulation. Previous studies have also shown that various types of primary afferents may trigger abnormal detection and pain responses among CRPS I patients.^{1,4,21,22} Verdugo and Ochoa¹ found warm hypoesthesia in 21 (33%) and cold hypoesthesia in 38 of 63 (60%) CRPS I patients. Cold and warm allodynia were observed in 9 of 63 patients (14%) each. Torebjörk *et al.*,²² on the other hand, diagnosed cold allodynia in 13 (65%) and warm allodynia in 4 of 20 (20%) CRPS I patients. All patients were found to have mechanical allodynia. Price *et al.*²¹ found warm allodynia in 17 of 31 (55%) CRPS I patients.

The different constellation of abnormalities suggest that the exact pathophysiology of each patient may differ between CRPS I patients. Thus, it seems wise to choose treatments based on the specific sensory abnormalities found in each patient. For example, sympathetic blocks that cause an increase of skin temperature seem inappropriate for patients with warm allodynia, whereas patients with mechanical allodynia are unlikely to profit from physical therapy. The relation between the mechanisms responsible for the symptoms of neuropathic pain, the molecular targets that underlie these mechanisms, current drug therapy of neuropathic pain, and the new agents in development all suggest specific therapies tailored to the specific symptoms of individual patients.²³

In summary, the current study has shown the following: (1) the validity of the relative approach, since contralateral homologous sides have approximately the same sensitivity in healthy controls; (2) hypoesthesia and allodynia can be diagnosed by either the absolute or relative approach, whereas hyperesthesia and hypoalge-

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sia can only be identified with the relative approach; (3) the two approaches disagree in 20% of cases; (4) age and gender may influence the absolute but not the relative approach; (5) both approaches are comparable with regard to reproducibility; and (6) the most frequent diagnoses in CRPS I patients were cold allodynia and mechanical hypoesthesia and allodynia.

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