Bilateral Hypersensitivity to Capsaicin, Thermal, and Mechanical Stimuli in Unilateral Complex Regional Pain Syndrome

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ABSTRACT

Background: Complex regional pain syndrome is multifactorial. Exaggerated inflammatory responses to limb injury may be involved. The authors hypothesized that capsaicin-induced pain and neurogenic inflammation (skin perfusion and flare area) are increased in patients with complex regional pain syndrome compared with that in controls.

Methods: Twenty patients with unilateral upper-limb complex regional pain syndrome and 20 age-, sex-, and body mass index–matched controls participated. Topical capsaicin 5% was applied to the back of both hands for 30 min, and pain intensity was assessed on a visual analogue scale. A laser Doppler perfusion imager scanner estimated capsaicin-induced skin perfusion and flare area. Autonomic and small-fiber function was assessed by sensory testing, quantitative sudomotor axon reflex test, and vasoconstrictor responses.

Results: The authors found bilateral hypersensitivity to capsaicin ($P \leq 0.02$), skin fold ($P = 0.001$), joint pressure ($P < 0.0001$), cold ($P \leq 0.01$), and heat pain ($P \leq 0.04$) in patients compared with that in controls and thermal and mechanical hyperalgesia in the complex regional pain syndrome–affected hand compared with that in the unaffected hand ($P \leq 0.001$). The patients had normal capsaicin-induced flare areas, thermal detection thresholds, quantitative sudomotor axon reflex test, and vasoconstrictor responses.

Conclusions: The main finding is bilaterally increased capsaicin-induced pain in patients compared with controls. The flare response to capsaicin was normal, suggesting that the increased pain response was not due to increased neurogenic inflammation. The bilateral hypersensitivity to painful chemical, thermal, and mechanical stimuli not confined to the innervation area of a peripheral nerve or root cannot be explained by a regional change and may partly be due to central sensitization.

What This Article Tells Us That Is New

• Hyperalgesia to chemical, thermal, and mechanical stimuli was observed bilaterally in patients with unilateral complex regional pain syndrome when compared with control unaffected subjects
• Thermal and mechanical hyperalgesia were greater in the complex regional pain syndrome–affected compared with the contralateral hands
• The results suggest that central sensitization may explain some pain symptoms in patients with complex regional pain syndrome

What We Already Know about This Topic

• Complex regional pain syndrome is characterized by abnormal inflammatory responses in the affected limb

Complex regional pain syndrome (CRPS) is a chronic pain condition characterized by spontaneous and evoked pain to various stimuli and a series of autonomic disturbances. CRPS is considered to be a multifactorial disorder in which inflammation, peripheral and central sensitization, vasomotor dysfunction, and neuroplastic changes within the central nervous system are thought to be involved. The relative contribution of these different mechanisms to CRPS is not well understood, and there may be interindividual differences. However, one of the most consistent findings is an increased inflammatory response. An exaggerated inflammatory response ipsilateral to limb injury has been indicated previously. Thus, facilitated peripheral neurogenic inflammation with increased intradermal protein extravasation induced by peripheral transcutaneous electrical stimulation and increased vascular permeability for macromolecules has been demonstrated in the affected extremity. Similar changes have also been shown in rat models of CRPS, in which 4 weeks of distal tibia fracture and cast immobilization induced chronic unilateral hindlimb warmth, edema, facilitated spontaneous protein extravasation, and allodynia. Although these studies indicate unilateral neurogenic inflammation of the affected limb, other
findings suggest inflammatory changes in the unaffected limb. This is demonstrated by systemically increased venous levels of the calcitonin gene–related peptide, a bilateral increase in substance P–induced protein extravasation, and an electrically induced increase in axon reflex vasodilation. Thus, neurogenic inflammation may cause both regional and systemic peripheral sensitization in CRPS.

Neurogenic inflammation is mediated by the depolarization of small sensory afferents in the skin, mainly nociceptive C-fibers triggering the release of neuropeptides such as calcitonin gene–related peptide and substance P. Both peptides induce local inflammation with protein extravasation and vasodilatation and by the release of cytokines. Correspondingly, the skin levels of substance P, calcitonin gene–related peptide, and inflammatory cytokines are increased in CRPS.

Studies investigating neurogenic inflammation in CRPS mainly rely on electrical stimulation, which is a nonphysiological stimulus that surpasses the peripheral nociceptive receptors. In contrast, application of capsaicin to the skin represents a physiological stimulus to examine both peripheral and central sensitization. Topical or intradermally applied capsaicin induces pain and neurogenic cutaneous inflammation by exciting the transient receptor potential cation channel subfamily V member 1 expressed by peptidergic nociceptive C-fibers in the skin. The transient receptor potential cation channel subfamily V member 1 is a transducer ion channel that not only plays a role in inflammatory pain but also involved in neuropathic types of pain after peripheral nerve injury. Topical application of capsaicin and the associated axon reflex with a flare response is an indirect but objective parameter in the assessment of small-fiber function. The capsaicin response differs from the response to electrical stimulation, at least as regards the release of calcitonin gene–related peptide.

In the current study, we determined pain, flare area, and skin perfusion after physiological stimulation with topical capsaicin applied to the dorsal part of the hands. We hypothesized that capsaicin-induced pain, skin perfusion, and flare areas are increased in patients with CRPS compared with that in healthy age-, sex-, and body mass index (BMI)–matched controls. Measures of autonomic and small-fiber function were secondarily assessed.

Materials and Methods

Participants

Participants received written and oral information about the study and signed an informed consent document. The study was carried out in 2007 to 2008 according to the Declaration of Helsinki and approved by the Local Ethics Committee (No. 20050192), Viborg, Denmark, and the Danish Data Protection Agency. The experiment was registered in Clinicaltrials.gov (NCT00468390).

Caucasian patients with CRPS attending the Neuropathic Pain Clinic at Aarhus University Hospital, Aarhus, Denmark, and patients with CRPS in Jutland were recruited. Patients were required to have distal unilateral affection of an upper limb without contralateral symptoms and to fulfill the research diagnostic criteria for CRPS. Twenty patients with CRPS were included. Thirteen of the patients were at the same time included in another study with separate measurements and separate report of primary outcome to Clinicaltrials.gov before study start.

Twenty Caucasian healthy volunteers with a normal physical examination matched the patients with CRPS with respect to age, sex, and four BMI intervals (<18.5, 18.5 to 24.9, 25 to 29.9, and >30 kg/m²). Controls were recruited by advertising at Aarhus University Hospital, Aarhus, Denmark.

Exclusion Criteria

Exclusion criteria included: age less than 18 yr, abnormal electrocardiogram, cardiovascular disease (except hypertension), previous sympathectomy, malignancy, acute or chronic infections (including known human immunodeficiency virus infection), endocrine diseases, or other significant diseases. Pregnant or lactating women were excluded, as were patients with alcoholism or drug abuse.

Medical Pain History and Clinical Examination

The medical history was obtained, and the patients rated their spontaneous limb pain and their average and maximal spontaneous limb pain within the last 24 h on a numeric rating scale from 0 to 10 (0 = no pain and 10 = maximal imaginable pain). Each patient marked the area of spontaneous pain on a body chart. The neurological examination was supplemented with a sensory examination that mapped the areas of pinprick hyperalgesia and brush-evoked allodynia. Pinprick hyperalgesia was defined as increased pain induced by a von Frey monofilament (painful stimulus) (745 mN; Semmes-Weinstein, Stoelting, IL) and assessed in distributional steps of 10 mm. Brush allodynia or dysesthesia was induced by brushing at 5 cm/s (SENSELab, Brush-05; Somedic Sales AB, Hörby, Sweden) in similar steps.

Experimental Set-up

All tests were performed in the same succession: reaction time; mechanical pressure pain thresholds; 20 min of rest in supine position; skin temperature and flux during 5 min of rest, 5 min of mental arithmetic, deep inspirations; thermal quantitative sensory testing (QST); and measurement of sweat and capsaicin-induced pain, perfusion, and flare area. All tests were performed in randomized order at the affected and the unaffected hand in the patients and at the right and left hand in the controls.

Reaction Time

Reaction time was measured with a self-constructed electronic device. When the investigator induced a sound and a light randomly at 5- to 10-s intervals, the participant released a button as soon as the signals were perceived. For each hand, the reaction time was calculated as the average.
of five consecutive measurements. Reaction time for the CRPS-affected hand was used to correct thermal and mechanical thresholds recorded on the contralateral hand and vice versa.

**Mechanical Pressure Threshold**
Pressure pain thresholds were examined with a pressure algometer (Somedic AB; 30 kPa/s). The subject indicated the pain threshold by pressing a button with the contralateral hand. For joint pain threshold testing, the rod (1 cm²) was pressed perpendicularly against the skin above the proximal interphalangeal joint of the middle finger. For skin fold testing, a skin area of 1 cm² between the thumb and index finger was squeezed; see further methodological details in the study by Terkelsen et al. Due to a delayed response when pressing the stop button with the CRPS-affected hand, all pain thresholds were corrected for reaction time. The mean pain thresholds of three stimuli were corrected for reaction time measured on the contralateral hand (Estimated threshold – (Reaction time (s) times 30 kPa/s)).

**Skin Temperature and Skin Perfusion**
Skin flux and skin temperature on the pulp of the thumbs were continuously measured with a laser Doppler perfusion monitor (DRT4; Moor Instruments Ltd., Axminster, Devon, United Kingdom) during 5 min of rest, 5 min of mental arithmetic, and deep inspirations. Mental arithmetic was induced by the Paced Auditory Serial Addition Task consisting of an auditory presentation of random digits from 1 to 9 with an interval of 2.4 s between the digits. The subject’s task was to continuously express the sum of the last two digits. During deep inspirations, subjects were breathing deeply (high tidal volume) at a low frequency (5 min⁻¹) with an inspiration–expiration ratio of 1:3. Vasconstrictor responses during deep inspirations were calculated as: (mean of minimal perfusion during inspirations two to four)/5 min baseline perfusion.

**Thermal QST**
Warm and cold detection thresholds and heat and cold pain thresholds were estimated with a computerized thermal tester (Somedic AB) with a Peltier device of 12.5 cm². The stimulus intensity was gradually increased from 32°C (1°C/s, cutoff limits: 10° and 52°C) until the subjects pressed a response button at a specific thermal sensation. Thermal QST was performed on the dorsum of the hands between the first and second metacarpals (hairy skin) and on the radial palms at the thenar eminence (glabrous skin) according to a previous protocol. Mean thermal thresholds of three stimuli were corrected for reaction time measured at the contralateral hand (Estimated threshold – (Reaction time (s) times 1°C/s)).

**Sweat Recording**
The quantitative sudomotor axon reflex test (QSART) (WR testworks ATL3, drug delivery electrode part no. 5191, measurement area 0.787 cm²; WR Medical Electronics Co., Stillwater, MN) was performed as previously described at the medial volar forearm 75% of the distance from the ulnar epicondyle to the pisiform bone symmetrical on both sides. Aqueous 10% (A6623; Sigma-Aldrich, Brøndby, Denmark) was iontophoresized (Iontophor-II, Model 6111PM/DX, 2 mA; Burnsville, MN) for 5 min. Humidity was recorded during iontophoresis and 5 min after the stimulation with subtraction of baseline sweat. Results were analyzed as area under the curve, maximal sweat production, and sweat onset latency. Moreover, spontaneous sweat secretion was measured bilaterally at the thenar eminence with a larger capsule (5.06 cm², WR part no. 5194) for 5 min, and the last minute was used as a measure of resting sweat output.

**Capsaicin-induced Pain and Flare Area**
Capsaicin 5% (100 µl; Unikem, Copenhagen, Denmark) was applied to the dorsum of both hands as previously described. Two patients with CRPS type 2 involving the ulnar nerves were included. Thus, to stimulate an area outside the primary lesioned nerve, capsaicin was applied dorsally in the innervation area of the radial nerve. During 30 min of topical capsaicin at a fixed skin temperature of 35°C, “time to sensory detection of capsaicin” and “pain onset” was recorded. Pain intensity ratings were assessed by means of a computerized visual analogue scale (0 = no pain and 100 = maximal imaginable pain). For each individual, pain intensity was continuously recorded (2 Hz) to estimate “area under the curve of pain,” “maximum pain,” and “time to maximum pain” (i.e., time when maximal pain is reached the first time). A laser Doppler perfusion imager scanner (LDI –2; Moor Instruments Ltd.) processed color-coded images (89 × 89 mm²; 256 × 256 pixels; 4 ms per pixel) of the superficial skin blood flow before application (baseline) and 1.5 min after removal of capsaicin (postcapsaicin image). The capsaicin-induced neurogenic flare was assessed offline (MoorLDI 5.2; Moor Instruments Ltd.). All pixels in the postcapsaicin images in which the perfusion unit exceeded the mean baseline plus twofold SD of the mean perfusion in the baseline picture were defined as capsaicin-induced flare and flux.

**Statistical Analysis**
To compare patients and controls (group effect) and to compare differences between the hands between the groups (interaction effect), a two-way ANOVA was performed. At significant group effect, a post hoc unpaired t test was performed to compare the unaffected hand in the patients with the matched control hand labeled “control 1.” Unequal variance t test was used for skin fold pain threshold and cold pain threshold in glabrous skin and cold detection threshold in hairy skin. At significant interaction, a post hoc paired t test was performed to test for differences between the hands in the patients and the controls. Correlations were tested with Spearman rank test. All statistical tests were two-sided, and the level of significance was 5%. Stata statistical software
(Version 12; StataCorp LP, College Station, TX) was used for statistical calculations.

Due to possible differences in pain thresholds between the right and left hand, the hands of the controls were matched to that of the patients. If the right hand was pain-free in the patient, the right hand in the control was labeled “control 1.” The match to the CRPS-affected hand was labeled “control 2.”

Results
Demographics
Twenty CPRS type 1 (n = 18) and type 2 (n = 2) patients (11 women, 9 men, right and left affected hand: 8/12; fig. 1) with mean age 45 yr (range, 18 to 72), BMI of 25.5 kg/m² SD 4.0, and mean systolic/diastolic blood pressure of 135/86 mmHg were included together with 20 age- (mean age, 44 yr; range, 19 to 68), sex-, and BMI-matched (25.5 kg/m² SD 4.7) controls with mean systolic/diastolic blood pressure of 127/81 mmHg (table 1). No demographic data differed apart from significantly more smoking patients (n = 8) than controls (n = 2).

Two controls were medicated with nonsedating histamine antagonists not taken the previous 2 days. Single healthy controls were medicated with tetracycline 500 mg/day, not taken the previous 2 days; levothyroxin 100 μg/day, not taken the previous day; citalopram 10 mg/day, not taken the previous 2 days; levothyroxin 100 μg/day, not taken the previous day; citalopram 10 mg/day, not taken the previous 2 days. Single healthy controls were medicated with tetracycline 500 mg/day, not taken the previous 2 days; levothyroxin 100 μg (contraceptive). Patient medication is reported in table 1.

Patient reports of pain rated on the numerical rating scale were (present): 4.8, range 0 to 9; (mean last 24 h): 6.2, range 1 to 9; (peak last 24 h): 8.2, range 4 to 10. Mean pain duration was 3 yr (range, 23 days to 17 yr). Thus, one patient with acute CRPS was included. Seventeen patients had a history of immobilization (table 1).

Capsaicin-induced Sensations, Flare Area, and Skin Perfusion
Two patients did not respond to the capsaicin application (capsaicin did not induce pain at any time point), and two patients did not complete the capsaicin test due to dystonia in one and severe capsaicin-induced pain on the unaffected hand in the other, leaving capsaicin data from 16 patients. In these patients, capsaicin was applied to an area with evoked and/or spontaneous pain in all except one (patient no. 10).

For technical reasons, the neurogenic flare area was not measured in one patient. Five controls were nonresponders, leaving capsaicin data from 15 controls. All other data were complete in the controls.

The differences between the hands were identical in patients and controls for pain, flare, and skin perfusion (table 2). Pain was rated significantly higher bilaterally in patients compared with that in controls; area under the curve (P = 0.04; mean [CI]: 20,748 cm²·s [1,335 to 40,161]), maximum pain (P = 0.02; mean [CI]: 18 [4 to 32]) (table 2 and fig. 2). For capsaicin-induced flare area, there was a group effect, but at post hoc testing, the flare area was not lower in the patients compared with the matched control hands (P = 0.059; mean [CI]: −7.7 [−15.7 to 0.3]). The mean capsaicin-induced flare area in patients with spontaneous pain in the application area (n = 5; mean 24.0 cm²) versus those without spontaneous pain in the area (n = 10; mean 25.0 cm²) was not significantly different (P = 0.82; mean [CI]: −1.1 [−11.3 to 9.1]). Two patients with CRPS type 2 were included. The values for the CRPS-affected hand versus the unaffected hand were: area under the curve (74,440 cm²/s/54,189 cm²·s); maximum pain (69/60); capsaicin-induced flare area (27.3 cm²/22.1 cm²).

For time to sensory detection of capsaicin, pain onset, time to maximum pain, and skin perfusion, there were no differences between patients and controls (table 2).

Reaction Time
The mean reaction time was higher for the CRPS-affected hand compared with that for the unaffected hand; no difference was seen when comparing with the control hands (table 3).

Mechanical Hyperalgesia to Joint and Skin Fold Pressure
Joint pressure and skin fold pain thresholds were reduced in the CRPS-affected hand compared with that for the unaffected hand; there were no differences between the control hands. There was a group effect with significantly lower thresholds when comparing the unaffected hand with the matched control hand (table 3 and fig. 3).

Heat and Cold Sensation
In both hairy and glabrous skin, there was no difference in thermal detection thresholds between patients and controls except for a significant group effect for cold detection at the dorsum of the hand; this difference was not seen at post hoc testing comparing the unaffected hand with the matched control hand (data not shown). In both hairy and glabrous skin, the CRPS-affected hand showed lower heat and cold pain thresholds compared with that in the unaffected hand. No differences were observed between the control hands. There was a group effect with lower heat and cold pain thresholds in patients compared with controls (table 3 and fig. 3). Thirteen versus 10 controls did not feel cold pain at 10°C (lower cutoff limits of thermal tester) in hairy and glabrous skin, respectively. At 10°C, four versus three patients did not feel cold pain at the unaffected hand in hairy and glabrous skin, respectively. In contrast, 10°C induced pain on the CRPS-affected hand in all patients.

Resting Sweat Output and QSART
Resting sweat output was complete for 18 patients and QSART latency and volume for 16 patients. Resting sweat output and QSART latency and volume did not differ between patients and controls (table 4).
Fig. 1. Spontaneous (marked red) and evoked pain (pinprick hyperalgesia and brush alldynia marked blue) in 20 patients with complex regional pain syndrome.
Table 1. Demographic Data and Medication in Patients with CRPS

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/Sex</th>
<th>Imm. (days)</th>
<th>Inciting Event, Affected Extremity</th>
<th>Pain Duration (days)</th>
<th>Medication NRS-24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46/M</td>
<td>3</td>
<td>Ulnar nerve compression, nerve conduction study, L. CRPS type 2</td>
<td>23</td>
<td>PCT 3g/day and ibuprofen 1.8g/day not taken the previous 12h.</td>
</tr>
<tr>
<td>2</td>
<td>48/M</td>
<td>35</td>
<td>Distal radius fracture, L</td>
<td>174</td>
<td>Escitalopram 20mg/day and oxazepam 15mg/day not taken previous 3 days. GBP 1.2g/day not taken previous 11 days.</td>
</tr>
<tr>
<td>3</td>
<td>18/F</td>
<td>156</td>
<td>Crush injury at the carpo-metacarpal joint of digit 1, L</td>
<td>183</td>
<td>PCT 2g/day not taken the previous 12h. Amitriptyline 25mg/day not taken the previous 3 days.</td>
</tr>
<tr>
<td>4</td>
<td>72/F</td>
<td>14</td>
<td>Crush injury of hand, L</td>
<td>279</td>
<td>Aspirin 75mg/day. Nabumetone 500mg/day. Potassium chloride 750mg/day. PCT 1.5g/day. Metoclopramide 10mg/day. Verapamil 80mg/day. Oxycodone sustained-release 60mg/day.</td>
</tr>
<tr>
<td>5</td>
<td>30/F</td>
<td>44</td>
<td>Strain of digit 1, L Previous CRPS in 1996 after strain of digit 1, L</td>
<td>359</td>
<td>PCT 4g/day, GBP 2.4g/day, desloratadine 5mg/day, oxycodone immediate-release 20mg/day, and ondansetron 12mg/day not taken the previous 12h.</td>
</tr>
<tr>
<td>6</td>
<td>48/M</td>
<td>173</td>
<td>Wrist injury with scapholunate ligament tear, R</td>
<td>368</td>
<td>Buprenorphine 2mg/day. GBP 1.6g/day not taken the previous 3 days. Isradipine 10mg/day. Bisoprolol 10mg/day. Spironolactone 50mg/day. Aspirin 100mg/day. Terazosin 2mg/day. Simvastatin 10mg/day. Picosulfate sodium. Bromazepam 6mg/day.</td>
</tr>
<tr>
<td>7</td>
<td>52/F</td>
<td>0</td>
<td>Carpal tunnel syndrome surgery, R. Intact median nerve</td>
<td>396</td>
<td>PCT 4g/day. Tramadol 150mg/day. Enalapril 10mg/day. Bendroflumethiazide 2.5mg/potassium chloride 573mg</td>
</tr>
<tr>
<td>8</td>
<td>44/F</td>
<td>0</td>
<td>Spontaneous, L arm</td>
<td>456</td>
<td>GBP 1.8g/day not taken the previous 6 days.</td>
</tr>
<tr>
<td>9</td>
<td>19/F</td>
<td>77</td>
<td>Surgical revision of ulcer, R hand</td>
<td>566</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>59/M</td>
<td>126</td>
<td>Clavicle fracture, R</td>
<td>786</td>
<td>PCT 4g/day and mirtazapine 15mg/day not taken the previous 11 days. GBP 1.6g/day not taken the previous 5 days.</td>
</tr>
<tr>
<td>11</td>
<td>38/M</td>
<td>28</td>
<td>Surgical decompression of ulnar nerve, L. CRPS type 2</td>
<td>791</td>
<td>PCT 2g/day and tramadol 300mg/day. Amitriptyline 25mg/day not taken the previous 10 days. GBP 2.4g/day not taken previous 3 days.</td>
</tr>
<tr>
<td>12</td>
<td>33/M</td>
<td>120</td>
<td>Spontaneous, L arm</td>
<td>918</td>
<td>Amitriptyline 75mg/day not taken the previous 12 days.</td>
</tr>
<tr>
<td>13</td>
<td>34/F</td>
<td>29</td>
<td>Crush injury with comminuted fracture and later amputation of digit 2, L</td>
<td>1,081</td>
<td>Oxycodone immediate-release 60mg/day, oxycodone sustained-release 20mg/day.</td>
</tr>
<tr>
<td>14*</td>
<td>38/F</td>
<td>0</td>
<td>Elbow trauma. Spinal cord contusion, R</td>
<td>1,129</td>
<td>PCT 2g/day. Ibuprofen 200mg/day not taken the previous 12h.</td>
</tr>
<tr>
<td>15</td>
<td>56/F</td>
<td>47</td>
<td>Distal radius fracture, R</td>
<td>1,211</td>
<td>—</td>
</tr>
<tr>
<td>16</td>
<td>39/M</td>
<td>86</td>
<td>Open luxation of distal interphalangeal joint of digit 1, R</td>
<td>1,358</td>
<td>—</td>
</tr>
<tr>
<td>17</td>
<td>62/F</td>
<td>28</td>
<td>Distal radius fracture, L</td>
<td>1,400</td>
<td>Levothyroxin 75 μg/day not taken the previous 1 day.</td>
</tr>
<tr>
<td>18</td>
<td>37/F</td>
<td>22</td>
<td>Arthroscopy of wrist joint after crush injury of wrist, L</td>
<td>1,971</td>
<td>PCT 4g/day. Codeine 100mg/day. Citalopram 60mg/day. Oxazepam 15mg/day.</td>
</tr>
<tr>
<td>19</td>
<td>63/M</td>
<td>20</td>
<td>Ligament reconstruction arthroplasty (Welby technique) digit 1, L</td>
<td>2,751</td>
<td>Ramipril 10mg/day. Simvastatin 40mg/day.</td>
</tr>
<tr>
<td>20</td>
<td>64/M</td>
<td>3</td>
<td>Hand infection after dog bite, R</td>
<td>6,235</td>
<td>Telfast 120mg/day not taken previous 4 days.</td>
</tr>
</tbody>
</table>

* Patient no. 14 had a spinal cord contusion and probably central pain, but additionally various autonomic phenomena were observed and reported and the patient fulfilled the research diagnostic criteria for CRPS. CRPS = complex regional pain syndrome; F = female; GBP = gabapentin; Imm. = immobilization; L = left; M = male; ND = no difference in skin temperature; Not cat. = not categorized; NRS-24h = the mean pain the last 24h rated on a numeric pain rating scale; PCT = acetaminophen; PGB = pregabalin; R = right.
Vasoconstrictor responses were complete for 19 patients. Vasoconstrictor responses to deep inspirations did not differ between patients and controls (table 4).

Correlation between Spontaneous Limb Pain and Hyperalgesia

We found no significant correlations between spontaneous pain and hyperalgesia on the CRPS-affected hand to joint pressure ($r = 0.02, P = 0.92$), skin fold ($r = -0.03, P = 0.88$), cold pain in glabrous ($r = -0.33, P = 0.15$) and hairy skin ($r = -0.32, P = 0.17$), and heat pain in glabrous ($r = 0.13, P = 0.57$) and hairy skin ($r = 0.37, P = 0.10$) (hyperalgesia was calculated as pain threshold on the CRPS-affected minus the unaffected hand).

Discussion

To our knowledge, this is the first study to investigate capsaicin-induced pain, skin perfusion, and flare area in patients with unilateral CRPS. The main finding in the current study is the bilateral increase in capsaicin-induced pain in patients compared with that in controls, suggesting that patients with CRPS have a general hypersensitivity to capsaicin in the upper limbs. The flare response after capsaicin induction was normal, suggesting that the increased pain after capsaicin induction probably involved other mechanisms than increased neurogenic inflammation.

The increased pain response was associated with bilateral thermal hyperalgesia in both glabrous and hairy skin as well as mechanical hyperalgesia. These findings suggest that the observed pain and bilateral hypersensitivity cannot be explained by a regional change. The changes are suggested to be due primarily to central sensitization, although peripheral sensitization may also play a role. The findings also suggest that one should be cautious when interpreting results from bilateral sensory testing in CRPS without including a control group.

In general, measures of small-fiber function such as capsaicin-induced flare area, thermal detection thresholds, QSART latency and volume, and vasoconstrictor responses were normal in this group of patients with CRPS. Therefore, peripheral nerve degeneration such as small-fiber neuropathy seems less likely, as also pointed out previously.1

Mechanism for Bilateral Hypersensitivity and Pain

Previous studies have found that signs and symptoms in CRPS may spread to more proximal sites with involvement of the entire limb or extend past the painful area of the affected limb in a hemisensory distribution.40,41 Symptoms may also spread to the contralateral side or even affect all four limbs.42,43 Correspondingly, in unilateral CRPS type 1, Huge et al.44 used QST and found bilateral sensory changes, and Vartiainen et al.45 found significantly lower pain thresholds after noxious laser stimulation applied to the dorsal CRPS-affected hand compared with the unaffected as well as with control hands.

Therefore, the mirror-like sensory hypersensitivity seen in the current study is well known in CRPS.42,46,47 Our patients
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had a bilateral increase in capsaicin-induced pain. Furthermore, they had heat and cold hyperalgesia in both glabrous and hairy skin and mechanical hyperalgesia to skin fold testing and joint pressure in the CRPS-affected hand compared with the contralateral hand as well as with the control hands. These findings are new because we demonstrate a generalized bilateral hypersensitivity to chemical, mechanical, and thermal stimuli affecting both hairy and glabrous skin, thus not respecting one peripheral nerve or root.

The precise mechanism of this generalized bilateral hypersensitivity to various sensory stimuli is unknown, but we believe the findings suggest that CRPS is not a regional disorder. The aggravated pain response was not associated with an increased axonal flare response. A preexisting discharge of nociceptors may deplete neuropeptides from the affected limb and thus reduce the axon reflex area similar to the changes in human immobilization. A comparison of flare areas in patients with versus without spontaneous pain did, however, not reveal a significant difference, suggesting that such depletion was not involved. Thus, regional or systemic neurogenic inflammation was not present in these patients with chronic CRPS.

The peripheral injury reported by 18 of the patients may have triggered peripheral sensitization and a long-lasting increase in the excitability of the central nervous system. However, from the current data, it is not possible to conclude whether central sensitization is triggered by neurogenic inflammation in the acute phase or by an ongoing systemic peripheral nociceptive sensitization.

The clinical presentation with dynamic and punctuate allodynia and pressure hyperalgesia suggests that elements of central sensitization are present. Moreover, we observed spread of pain sensitivity after Aβ-, C-, and Aδ-fiber stimulation across peripheral nerves and nerve root territories to areas without demonstrable pathology as well as contralateral hypersensitivity to capsaicin in the absence of inflammatory changes or peripheral trauma. Eight patients had cold pain thresholds greater than 20°C in an area without any obvious pathology and with intact detection thresholds on the unaffected hand. This can hardly be explained by peripheral sensitization. We found no correlation between spontaneous pain perception and evoked pain responses suggests that these measures describe different aspects of the pain. The clinical expression of this diversity is illustrated by patients with spontaneous pain who avoid pain aggravation by immobilizing the extremity.

### Table 3. Thermal and Mechanical Pain Thresholds in Patients and Controls

<table>
<thead>
<tr>
<th></th>
<th>CRPS</th>
<th>Control</th>
<th>ANOVA</th>
<th>Post Hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Between-group Interaction</td>
<td>Between Hands (CRPS)</td>
<td>Patients vs. Controls</td>
<td></td>
</tr>
<tr>
<td>Reaction time (s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain-free hand</td>
<td>0.22 (0.02)</td>
<td>0.21 (0.03)</td>
<td>0.045 0.02</td>
<td>0.01 0.42</td>
</tr>
<tr>
<td>CRPS hand</td>
<td>0.27 (0.09)</td>
<td>0.22 (0.04)</td>
<td>&lt;0.0001 0.0004</td>
<td>0.05 (0.01–0.08) 0.007 (−0.01 to 0.02)</td>
</tr>
<tr>
<td>Pain threshold at skin folding (kPa)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain-free hand</td>
<td>362 (126)</td>
<td>600 (270)</td>
<td>&lt;0.0001</td>
<td>−172 (−228 to −117) −238 (−373 to −103)</td>
</tr>
<tr>
<td>CRPS hand</td>
<td>190 (132)</td>
<td>591 (275)</td>
<td>&lt;0.0001 0.005</td>
<td>−143 (−197 to −89) −283 (−368 to −197)</td>
</tr>
<tr>
<td>Joint pain threshold (kPa)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain-free hand</td>
<td>315 (106)</td>
<td>597 (156)</td>
<td>&lt;0.0001</td>
<td>−0.0001</td>
</tr>
<tr>
<td>CRPS hand</td>
<td>172 (98)</td>
<td>569 (154)</td>
<td>&lt;0.0001 0.005</td>
<td>−0.0001</td>
</tr>
<tr>
<td>Cold pain threshold (glabrous skin) (°C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain-free hand</td>
<td>16.6 (6.3)</td>
<td>12.3 (3.6)</td>
<td>&lt;0.0001</td>
<td>6.7 (4.0 to 9.4) 4.2 (0.9 to 7.5)</td>
</tr>
<tr>
<td>CRPS hand</td>
<td>23.2 (5.7)</td>
<td>12.1 (3.0)</td>
<td>&lt;0.0001 0.005</td>
<td>0.005</td>
</tr>
<tr>
<td>Cold pain threshold (hairy skin) (°C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain-free hand</td>
<td>17.7 (6.7)</td>
<td>12.3 (4.7)</td>
<td>&lt;0.0001</td>
<td>5.7 (3.0 to 8.3) 5.5 (1.8 to 9.2)</td>
</tr>
<tr>
<td>CRPS hand</td>
<td>23.4 (5.5)</td>
<td>11.3 (2.5)</td>
<td>&lt;0.0001 0.001</td>
<td>0.0003</td>
</tr>
<tr>
<td>Heat pain threshold (glabrous skin) (°C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain-free hand</td>
<td>41.2 (4.2)</td>
<td>45.2 (3.3)</td>
<td>&lt;0.0001</td>
<td>−3.0 (−4.4 to −1.7) −4.0 (−6.4 to −1.6)</td>
</tr>
<tr>
<td>CRPS hand</td>
<td>38.1 (4.5)</td>
<td>45.1 (3.1)</td>
<td>&lt;0.0001 0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>Heat pain threshold (hairy skin) (°C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain-free hand</td>
<td>41.3 (4.1)</td>
<td>44.0 (3.8)</td>
<td>&lt;0.0005 0.001</td>
<td>0.001 0.04</td>
</tr>
<tr>
<td>CRPS hand</td>
<td>38.4 (4.1)</td>
<td>44.3 (3.3)</td>
<td>&lt;2.9 (−4.5 to −1.3) −2.7 (−5.1 to −0.2)</td>
<td></td>
</tr>
</tbody>
</table>
Fig. 3. Thermal and mechanical sensory testing. Patients with complex regional pain syndrome (CRPS) had mechanical hyperalgesia to skin fold testing (A) and to joint pressure (B) on the affected hand (CRPS) compared with the contralateral pain-free hand (pain-free) and on the pain-free hand compared with controls. They had thermal hyperalgesia to cold pain in glabrous (C) and hairy skin (D) and to heat pain in glabrous (E) and hairy skin (F) on the affected hand (CRPS) compared with the contralateral pain-free hand (pain-free) and on the pain-free hand compared with controls. Control 1 = the hands in the controls matching the pain-free hand in the patients; control 2 = the hands in the controls matching the CRPS hand in the patients. Significant changes are indicated by asterisks.
Supraspinal mechanisms including neuroplastic changes within the central nervous system are well known in CRPS. Central changes are demonstrated by adaptive changes in the thalamus contralateral to the CRPS-affected limb with acute thalamic hyperperfusion and chronic thalamic hyperperfusion.50 There is reports of significant shrinkage and reorganization of the somatosensory cortical hand representation contralateral to the CRPS-affected painful arm,50 reversed after successful treatment.51 Other studies have demonstrated bilaterally disturbed inhibition in the central motor-sensory network52 and dysfunction of endogenous pain modulation with facilitation of nociceptive inputs.53 Finally, an increased attentional response to painful stimuli may also play a role.54

Taken together, the bilateral changes suggest that CRPS is not a regional disorder. The generalized hypersensitivity may be explained mainly by central sensitization although systemic peripheral sensitization may also be involved.

**Limitations**

All significant measures in the current study depend on subjective responses. In future studies, one could argue for the use of, for example, contact heat- and cold-evoked potentials,55 noninvasive and objective tests to explore thermal and nociceptive pathways that bypass the subjective report and are independent of reaction time.

Emotional states are known to modulate human pain reactivity, and pain thresholds are reduced by anxiety56 and depression,57 which are well-known comorbidities in CRPS58 and may have affected the pain thresholds.

The differences in mechanical and thermal thresholds were secondary outcome measures. However, the differences were surprisingly large, and except for cold pain threshold in glabrous skin and heat pain threshold in hairy skin compared between patients and controls, control for multiple comparisons does not make the results nonsignificant. In fact, cold hyperalgesia might be underestimated because more patients than controls felt pain at the 10°C cutoff limit of the thermotester.

It was not possible to match medication status in patients and controls. To reduce this source of error, some drugs were avoided in a relevant time interval before the experimental sessions. However, the significant higher capsaicin-induced pain and lower pain thresholds in patients compared with controls might be underestimated due to analgesics taken by the patients.

The order of testing was always the same, raising the possibility that the results in the latter tests were dependent on the former tests. To reduce this error, the hand order was randomized for all tests and capsaicin was applied as the last measure.

Capsaicin was applied topically to be able to discontinue the experiment in case of intolerable pain levels; this was the case in two patients. Five controls and two patients did not develop pain, which could be due to reduced percutaneous penetration and reduced stimulation of the peripheral nociceptors; the nonresponders were therefore excluded. We considered it unethical to test the capsaicin response in the patients before the experiment.

Quantitative sensory testing was performed in all participants, whereas the capsaicin test and QSART were performed in 16 patients and the capsaicin test in 15 controls. As such, the sample size becomes small with an already heterogeneous population of patients.

We expected similar mechanisms in CRPS type 1 and in the area of spreading symptoms not innervated by the lesioned nerve in CRPS type 2 and included two patients with CRPS type 2. The primary outcome, capsaicin-induced pain, and flare area were of same magnitude as measures for CRPS type 1.

**Strengths**

Quantitative sensory testing and autonomic measures depend on age, sex, BMI, specific region and side tested,57,59 the succession by which stimuli are applied to the painful versus the pain-free side, training status of the experimenter, response time of the participant, etc. The strengths of the current study are the strictly standardized conditions controlling these factors by comparing the CRPS-affected hand with the contralateral unaffected hand as well as control hands in age- and sex-matched controls. The testing started randomly at the right and left hand and at the CRPS-affected and CRPS-unaffected hand. All QSTs were performed by the same trained physician, and thermal and mechanical thresholds were corrected for response time because the patients reacted more slowly with the CRPS-affected hand.

### Table 4. Resting Sweat Output, Quantitative Sudomotor Axon Reflex Test, and Vasoconstriction in Patients with CRPS and Controls

<table>
<thead>
<tr>
<th></th>
<th>CRPS</th>
<th>Controls</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CRPS Hand</td>
<td>Pain-free Hand</td>
<td>Control 1</td>
</tr>
<tr>
<td>RSO (μl)</td>
<td>0.328 (0.103)</td>
<td>0.370 (0.102)</td>
<td>0.343 (0.118)</td>
</tr>
<tr>
<td>QSART (latency) (s)</td>
<td>122 (35)</td>
<td>122 (27)</td>
<td>135 (34)</td>
</tr>
<tr>
<td>QSART (vol) (μl)</td>
<td>0.847 (0.438)</td>
<td>0.921 (0.436)</td>
<td>1.089 (0.792)</td>
</tr>
<tr>
<td>Inspiration (vasoc.)(%)</td>
<td>72 (56)</td>
<td>61 (29)</td>
<td>63 (37)</td>
</tr>
</tbody>
</table>

Values are presented as mean (SD).

Control 1 = the hand in the control matching the pain-free hand in the patient; control 2 = the hand in the control matching the CRPS hand in the patient; CRPS = complex regional pain syndrome; Inspiration (vasoc.) = vasoconstrictor response to deep inspiration; QSART = quantitative sudomotor axon reflex test; QSART (latency) = QSART response latency; QSART (vol) = QSART total volume measured during 5 min iontophoresis and 5-min poststimulation; RSO = resting sweat output measured during 1 min.

CRPS = complex regional pain syndrome; Inspiration (vasoc.) = vasoconstrictor response to deep inspiration; QSART = quantitative sudomotor axon reflex test; QSART (latency) = QSART response latency; QSART (vol) = QSART total volume measured during 5 min iontophoresis and 5-min poststimulation; RSO = resting sweat output measured during 1 min.
Summary
The main finding in this group of selected patients with unilateral upper-limb CRPS is a bilateral increase in capsaicin-induced pain response in comparison with that in controls. The flare response to capsaicin was normal, suggesting that the increased capsaicin-induced pain was not due to increased neurogenic inflammation. The bilateral hypersensitivity to painful chemical, thermal, and mechanical stimuli not confined to the innervation area of a peripheral nerve or root cannot be explained by a regional change and may in part be due to central sensitization.

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Competing Interests
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