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Retrospective Review

Thermal Pain in Complex Regional Pain Syndrome Type I

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Background: Quantitative sensory testing (QST), with thermal threshold determinations, is a routine part of the comprehensive clinical workup of patients suffering from chronic pain, especially those with Complex Regional Pain Syndrome seen at our outpatient pain clinic. This is done to quantitatively assess each patient's small fiber and sensory function in a controlled manner. Most patients have normal sensory detection thresholds, but there are large differences in thermal pain thresholds. Some patients display no thermal hyperalgesia, while other patients display severe thermal hyperalgesia when tested in all 4 limbs.

Objectives: To ascertain the prevalence of thermal hyperalgesia in patients with complex regional pain syndrome type 1 (CRPS-I).

Study Design: This was a retrospective review of the results of QST performed on 105 patients as part of their clinical workup.

Setting: The outpatient clinic of the Department of Neurology at Drexel University College of Medicine.

Methods: All patients had a diagnosis of CRPS-I. Thermal quantitative sensory testing, including cool detection, warm detection, cold pain, and heat pain, was performed on 8 distal sites on each patient as part of a comprehensive clinical examination.

Results: With regards to thermal hyperalgesia, patients with CPRS-I appear to fall into distinct groups. One subgroup displays evidence of generalized cold and heat hyperalgesia, one subgroup displays evidence of generalized cold hyperalgesia only, one displays evidence of heat hyperalgesia only, and one subgroup does not display evidence of cold or heat hyperalgesia.

Limitations: This study is based on retrospective information on a relatively small (105 patient records) number of patients. Since only patients with CRPS-I were included, the results are only applicable to this group.

Conclusions: Thermal QST provides useful information about the sensory phenotype of individual patients. Subgrouping based on thermal hyperalgesia may be useful for future studies regarding prognosis, treatment selection, and efficacy.

Key words: Complex regional pain syndrome, CRPS, quantitative sensory testing, QST, cold pain, heat pain, thermal hyperalgesia

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Complex regional pain syndrome (CRPS) is a very debilitating chronic pain disorder which has been the subject of recent reviews (1,2). The most prominent aspect of the disease is that pain is out of proportion to any inciting event. As well as spontaneous unprovoked pain, there is often the presence of exaggerated responses to painful stimuli, hyperalgesia, and a painful response to normally non-painful thermal or mechanical stimuli.

There is significant variability in the clinical presentation of the disease. It is often difficult to obtain accurate information about the functioning of the sensory systems, since standard electrophysiological testing, such as electromyography and nerve conduction studies, provide information about large, fast conducting nerve fibers only. These fibers conduct predominantly low threshold mechano reception and motor efference.

Quantitative sensory testing (QST) uses a variety of psychophysical methods to obtain quantitative and reproducible information regarding the function of the sensory systems. The detection of cool or cold stimulation is believed to be mediated by a subset of polymodal C-fibers and thinly myelinated A-delta fibers, the latter also is thought to be the mediator of the sharp, first component of pain. Warm or hot perception is thought to be primarily mediated by the small, non-myelinated slow conducting C fibers, which mediate burning pain.

In our clinic, QST is a routine part of the clinical workup of many chronic pain patients, especially those with CRPS. This is done to document, in as a controlled a fashion as possible, dysfunction of the nervous system, specifically small fiber mediated sensory systems.

The purpose of this paper was to determine the prevalence of thermal hyperalgesia in patients with CRPS-I, and whether thermal hyperalgesia may provide a basis for subcategorizing these patients.

Methods

This was a retrospective review of test records from charts of patients who suffered from CRPS which was approved by the Drexel University Institutional Review Board. All patients were being treated at the Drexel pain clinic by the same physician (RJS). Results from patients seen in the clinic in the year 2009 who met the clinical criteria for CRPS-I (3) were included. All patients had continuing pain out of proportion to any citing event, reported at least one symptom in 3 out of the 4 cardinal symptoms (sensory, vasomotor, sudomotor/edema, motor/trophic), as well as displaying at least one sign in 2 or more of these 4 categories at the time of their initial office visit. The diagnosis of CRPS-I was used for patients who did not display evidence of major nerve damage, meaning that electomyographic and nerve conduction studies were negative. Information regarding medications and duration of CRPS was obtained from the patient's medical chart.

These patients had subsequently received QST as part of their clinical workup with the results placed in their medical chart. A total of 105 patient records (81 women, 24 men) were the basis of this study.

All testing had been done in a room with ambient temperature between 23 – 25°C. A Medoc TSA-II Thermosensory analyzer (WinTSA 5.24, Ramat Yishai, Israel) with a 3 cm by 3 cm thermode was used. The sites tested on all patients were the thenar eminence and the hypothenar eminence on the hands (median and ulnar sensory nerve territories) in the upper extremity, and the medial and the lateral aspect of each foot (L4 and S1 territories).

A baseline temperature of 32°C and a cooling rate of -1.0°C per second were used for all tests of cool detection threshold (CDT) and cold pain (CP). The maximum cold temperature achievable was -9.9°C, which is equivalent to a change of -41.9°C from baseline. For warm detection threshold (WDT) and heat pain (HP), the same baseline temperature of 32°C and warming rate of +1.0°C per second were used. The maximum heat temperature achievable was 50.0°C, which is equivalent to a +18.0°C increase from baseline. For cool and warm detection threshold determinations, the patients were instructed to press the response button when they first detected a sensation of cooling or warming respectively. For clinical purposes of determining evidence of thermal sensory detection dysfunction, the normal cutoff limits provided by Yarnitsky (4) were used.

For cold and heat pain determinations the patients had been instructed to press the response button when either the cooling stimulation or heat stimulation became painful. The thermode immediately returned to baseline (32°C) after the button was pressed.

The order of testing at each site was 3 trials of CDT, 3 trials of WDT, 2 trials of CP, and 2 trials of HP. This order was chosen so that detection thresholds would not be affected by prior painful stimulation (5).

The cutoff for normal CP threshold was chosen to be changes of greater than -7.0°C from baseline (temperatures less than less 25.0°C). This value was chosen based on a published study of CP in control subjects (6) and also because the temperature for activation of the sensitive cold thermoreceptor TRPM8 is estimated to be about 25°C (7). A change of less than -7.0°C from baseline (temperatures greater than 25°C) reported as causing pain was taken as evidence of cold allodynia at that site.

For HP, values of greater than or equal to +7.5°C from baseline (39.5°C) for the hands and greater than +9.0°C from baseline (41.0°C) for the feet were considered normal (8). Values less than these were considered to be evidence of heat hyperalgesia.

The averages for each of the 8 tested sites were calculated and statistical comparisons were done using

Microsoft Office Excel 2003 (Microsoft Corporation, Redmond, WA).

Results

The thermal QST results of 105 CRPS patients were reviewed. There were no statistically significant differences with regards to cold or heat pain thresholds when the average values from the 8 sites tested for the entire group of CRPS patients was compared to values from historical controls for this lab ($P > 0.1$ for all 8 sites, Fig. 1).

As the test results of these patients were reviewed it became apparent that with regards to thermal induced pain there appeared to be distinct subgroups, those with no evidence of cold or heat hyperalgesia, and those who had evidence of severe cold and/or heat hyperalgesia.

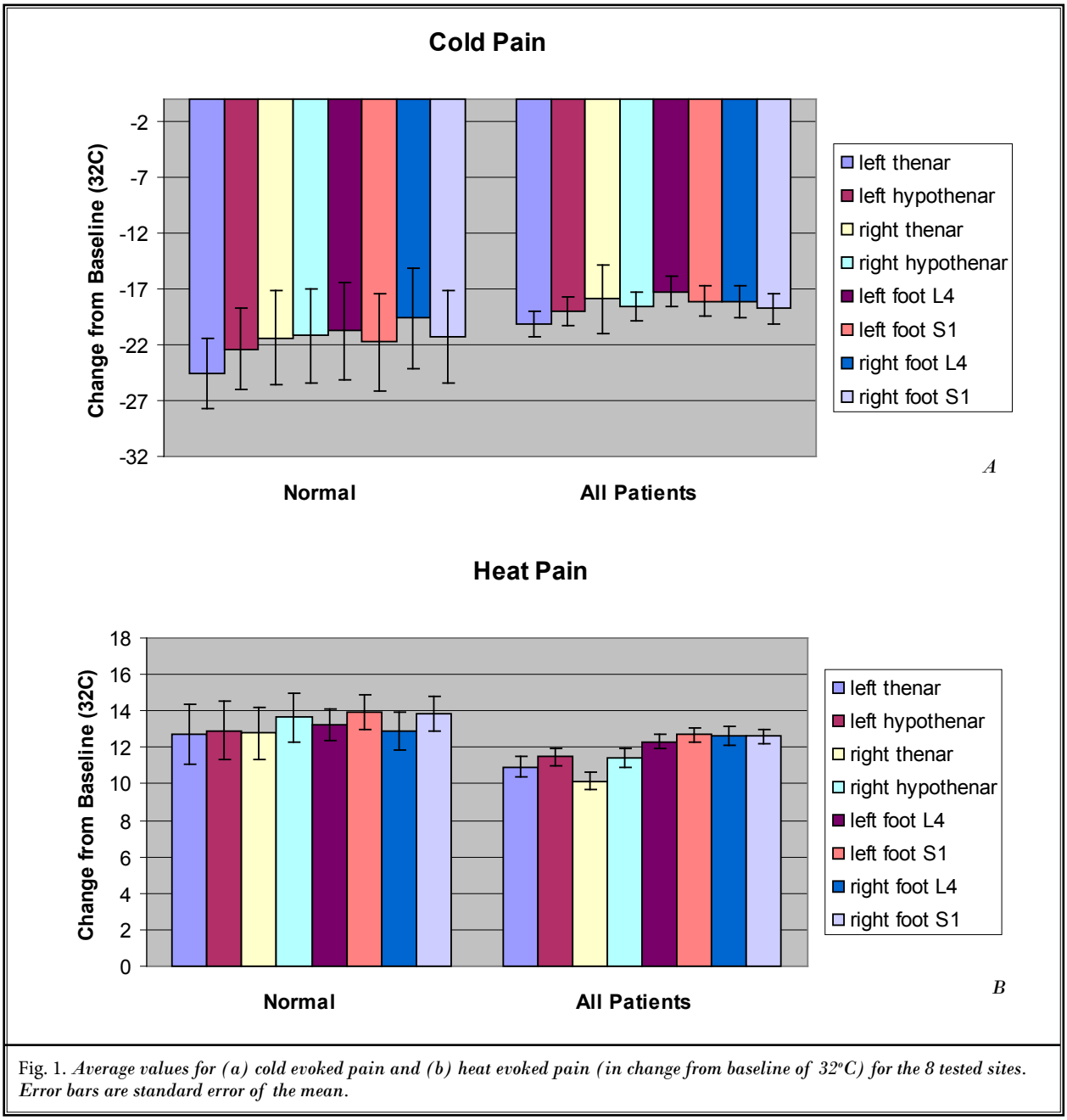


Fig. 1. *Average values for (a) cold evoked pain and (b) heat evoked pain (in change from baseline of 32°C) for the 8 tested sites. Error bars are standard error of the mean.*

Based on this observation, patients were each placed into one of 4 possible groups with respect to evoked thermal pain. Patients placed into Group 1 were those who displayed no evidence of cold allodynia or of heat hyperalgesia at any of the 8 tested sites. This group accounted for 39% of the total (Table 1). Patients placed into Group 2 consisted of those who displayed evidence of cold allodynia at one or more tested sites, but displayed no evidence of heat hyperalgesia at any of the 8 sites. This group made up 14% of the total. Patients placed into Group 3 were those who displayed evidence of heat hyperalgesia at one or more tested sites, but displayed no evidence of cold allodynia at any of the tested sites. They made up 7% of the total. Patients placed into Group 4 were those who showed evidence of cold allodynia and evidence of heat hyperalgesia at one or more of the 8 sites tested, and not necessarily the same sites. This group made up 40% of the total (Table 1).

The average values for CDTs, WDTs, CP, and HP for each of the 8 tested sites were calculated for each of the 4 groups. Results for thermal pain for all of the patients are shown (Fig. 2), and results for just the female patients are also shown separately (Fig. 3). The results of paired Student T-test comparisons of CDT, WDT, CP, and HP between Group 1 and each of the other 3 groups is tabulated and presented (Table 2). As can be seen in the table, there were no significant differences in the cool or warm detection thresholds between the groups, only thermal pain showed significant differences.

Discussion

We routinely perform QST on patients who are seen at our pain clinic. We believe that a formal test of sensory function under controlled conditions and standardized protocols provides a useful starting point in the assessment of chronic pain patients. This is especially true in the case of patients suffering from CRPS, most of whom have been seen by multiple health care providers prior to presentation at our clinic. CRPS is still largely a diagnosis of exclusion and as such has a variable clinical presentation. Since there is no definitive or objective test for CRPS, QST provides at least one common standardized measure of an individual's subjective response to testing that is aimed specifically at some of the most troubling symptoms of the painful condition. The results can be compared to other patients and can also be used to follow a patient over time. Most patients find the testing to be a positive experience. Many have expressed that they feel the QST is the one test that directly addresses the chief complaint of hypersensitivity, a common feature of CRPS.

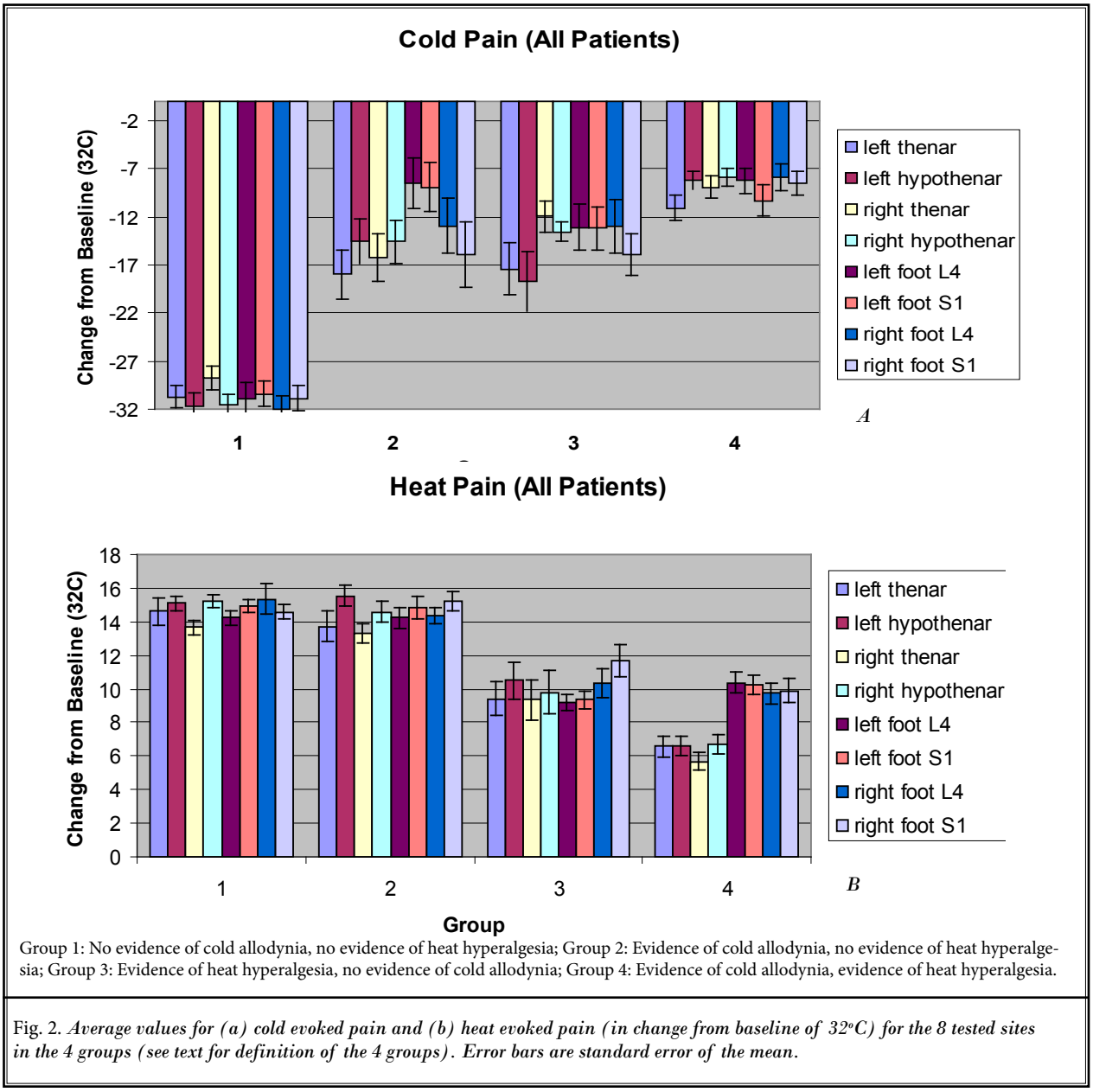
For any test that uses psychophysical methodology, such as thermal QST, it is critical that the testing is conducted in the most standardized way possible. Room temperature, thermode contact, alertness, standardized instructions that are fully understandable, and lack of positive or negative feedback from the person administering the tests are among the variables that need to be controlled. For thermal QST, as well as any test of neurological function, to be useful in the diagnostic workup of patients, every effort must be made to maintain consistency of testing. This we believe is the case with our QST procedures.

We also believe that our approach of routinely testing at least the 8 sites described in this report may be more clinically useful than the approach used in other recently published studies (9,10). In the German Research Network on Neuropathic Pain studies, the most affected area is compared to the contralateral side (10).

Table 1. *CRPS patients subdivided into groups with respect to thermal evoked pain at 8 tested sites.*

	Group 1	Group 2	Group 3	Group 4
Number of patients (105 total)	41 (26F, 15M) (39% of total)	15 (10F, 5M) (14% of total)	7 (7F, 0M) (7% of total)	42 (38F, 4M) (40% of total)
Age (std. dev.)	43.6 (±11.9)	48.7 (±9.1)	36.8 (±7.2)	43.2 (±11.8)
Pain years (std. dev.)	8.0 (±9.6)	12.7 (±15.3)	8.8 (±5.9)	7.8 (±7.0)
Opiate use data available	27 (18F, 9M)	11 (9F, 2M)	5 (5F, 0M)	32 (30F, 2M)
Currently on opiates	13 (7F, 6M) 48%	6 (5F,1M) 54%	3 (3F, 0M) 60%	19 (18F, 1M) 59%

Group 1: No evidence of cold allodynia (CA), no evidence of heat hyperalgesia (HH); Group 2: Evidence of cold allodynia, no evidence of heat hyperalgesia; Group 3: Evidence of heat hyperalgesia, no evidence of cold allodynia; Group 4: Evidence of cold allodynia, evidence of heat hyperalgesia.



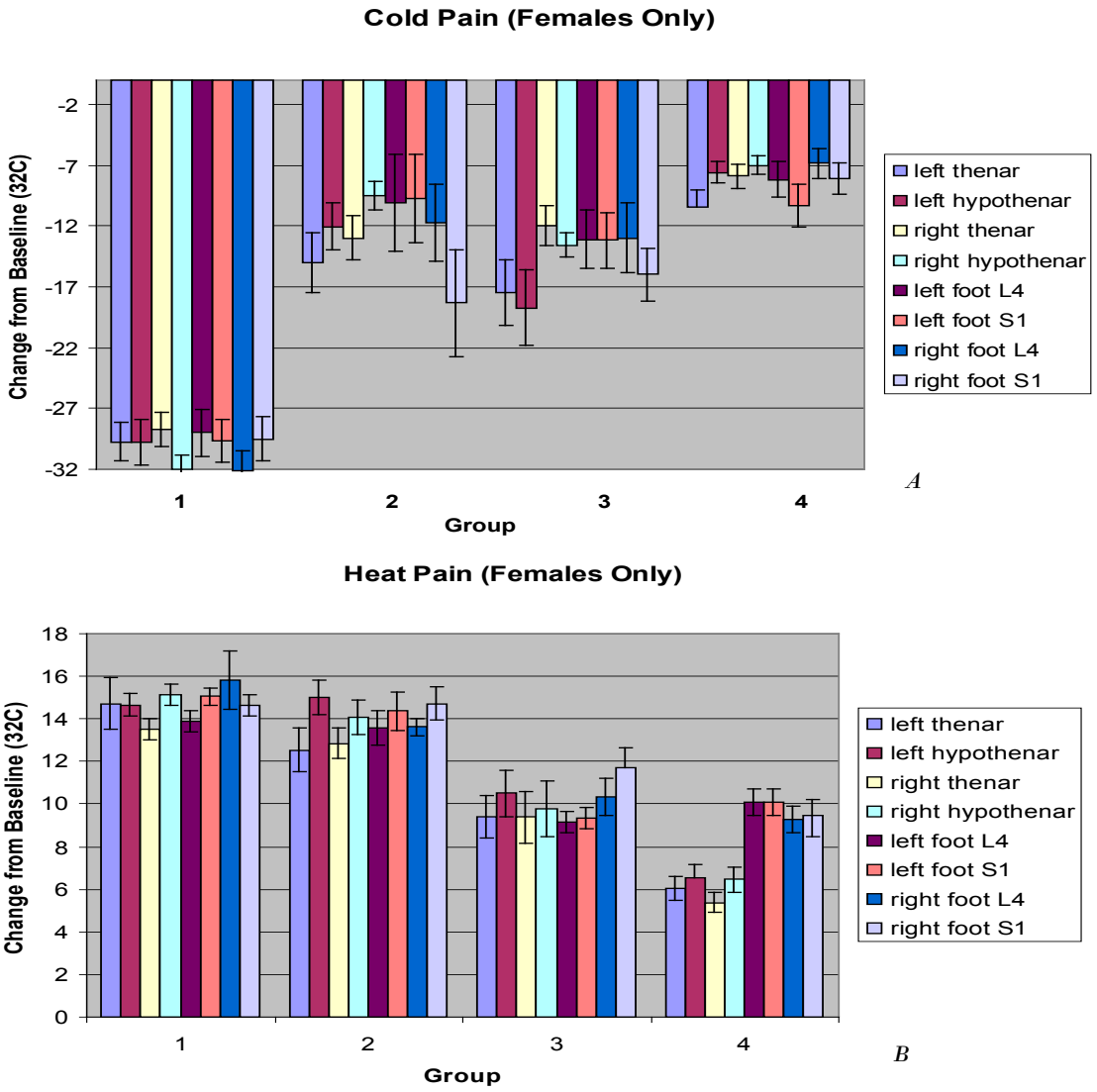
Group 1: No evidence of cold allodynia, no evidence of heat hyperalgesia; Group 2: Evidence of cold allodynia, no evidence of heat hyperalgesia; Group 3: Evidence of heat hyperalgesia, no evidence of cold allodynia; Group 4: Evidence of cold allodynia, evidence of heat hyperalgesia.

Fig. 2. *Average values for (a) cold evoked pain and (b) heat evoked pain (in change from baseline of 32°C) for the 8 tested sites in the 4 groups (see text for definition of the 4 groups). Error bars are standard error of the mean.*

However, in the case of CRPS, the contralateral side may be affected, as the disease frequently spreads in a mirror distribution (11). Also, in our experience, CRPS patients often state that their pain varies significantly, such that the most painful area is not always the same and often not the site where the initial pain occurred.

Using the criteria described in the methods section to set cutoff temperatures for an operational definition of cold allodynia and heat hyperalgesia, we found that the 40% of CRPS patients who made up Group 4 (Table 1) display what appears to be a generalized thermal hypersensitivity. In this group 81% (34 out of 42 patients) displayed severe cold allodynia (using the strict cutoff value of a less than -7°C change from baseline) in more than one quadrant with 74% of the group demonstrating this severe cold allodynia in both upper and lower limbs. Heat hyperalgesia was present in more than one quadrant in 79% of this group, with 62% demonstrating heat hyperalgesia in both upper and lower limbs.

The cold allodynia presenting in the 14% of CRPS



Group 1: No evidence of cold allodynia, no evidence of heat hyperalgesia; Group 2: Evidence of cold allodynia, no evidence of heat hyperalgesia; Group 3: Evidence of heat hyperalgesia, no evidence of cold allodynia; Group 4: Evidence of cold allodynia, evidence of heat hyperalgesia.

Fig. 3. *Average values for (a) cold evoked pain and (b) heat evoked pain (in change from baseline of 32°C) for the 8 tested sites in the 4 groups (see text for definition of the 4 groups). Error bars are standard error of the mean.*

patients who comprise Group 2 (Table 1) appears to be less generalized than that of Group 1. Only one-third of Group 2 display severe cold allodynia in a combination of upper and lower limbs. While it is beyond the scope of this paper, it is intriguing to consider that there may be pathological differences between patients who display cold allodynia in the presence of heat hyperalgesia, and those who display cold allodynia in the absence of coexistent heat hyperalgesia.

Cold induced pain has been the subject of previous studies (20-23).

One posited mechanism states that cold allodynia could result from the presence of a concomitant cool thermal sensory deficit which would hypothetically reduce the normal inhibitory function of cool conducting A-delta fibers on cold responsive C nociceptive

Table 2. *Results of paired Student t-test comparisons of detection and pain thresholds.*

	Group 1 (n = 41)		Evidence Results
Group 4 (n = 42)			
CDT	NS	(8/8 sites)	Evidence of cold allodynia, evidence of heat hyperalgesia.
WDT	NS	(8/8 sites)	
CP	$P < 0.001$	(8/8 sites)	
HP	$P < 0.001$	(8/8 sites)	
Group 3 (n = 7)			
CDT	NS	(8/8 sites)	Evidence of heat hyperalgesia, no evidence of cold allodynia
WDT	NS	(8/8 sites)	
CP	$P < 0.001$	(8/8 sites)	
HP	$P < 0.001$	(5/8 sites)	
Group 2 (n = 15)			
CDT	NS	(8/8 sites)	Evidence of cold allodynia, no evidence of heat hyperalgesia
WDT	NS	(6/8 sites)	
CP	$P < 0.001$	(8/8 sites)	
HP	NS	(8/8 sites)	

NS (not significantly different, P > 0.05); CDT (cool detection threshold); WDT (warm detection threshold); CP (cold pain threshold); HP (heat pain threshold); Group 1: No evidence of cold allodynia, no evidence of heat hyperalgesia

fibers (23). Although we cannot definitively rule out this mechanism, only 5 patients (out of 42 patients in Group 4) demonstrated evidence of this type of cold allodynia. In only these 5 was there evidence of abnormally increased CDT and abnormally decreased cold pain threshold at the same site. The majority of patients appear to have normal CDT with the cold allodynia at a given site. This would indicate that the cold hypersensitivity in most of the patients in Group 4 is more likely the result of sensitization of cold C nociceptive fibers or central sensitization.

A previous study using the same thermal testing methods described in this retrospective study determined thermal thresholds for patients with chronic pain from brachial plexus traction injury (BPTI) (15). The average cold pain thresholds, in degrees change from a baseline of 32°C, in thenar and hypothenar sites for controls in this study was -28.65 ± 2.86°C and -28.33 ± 3.70°C, respectively. The thresholds for thenar and hypothenar in the most affected side in BPTI patients -24.32 ± 5.93°C and -22.93 ± 6.49°C, respectively, was significantly different (15), but not to the same degree as the CRPS patients in Group 4 of this study. Heat pain thresholds for control thenar and hypothenar eminences and for those of BPTI patients did not differ significantly. The severe cold and heat hypersensitivity displayed by the CRPS patients in Group 4 seems to be unique for this subgroup of CRPS patients.

At least one study with thermal QST has shown that women in general have more sensitive thresholds to cold and heat pain (9). One might argue that the larger percentage of men in Group 1 than in Group 4 might have an influence on the large differences in thermal pain for the 2 groups. This appears unlikely since the large differences in cold and heat pain thresholds between the groups is almost identical when the data for all patients is compared to the data for women patients only (Figs. 2 and 3).

The possibility that exacerbation of generalized thermal hyperalgesia or cold allodynia might be due to opiate usage needs to be addressed. A number of papers demonstrate that chronic use of opiates can cause or exacerbate hyperalgesia (16-18). A significant decrease in cold pain tolerance has been documented after one month of opiate treatment (19). It is less likely that opiate use is a major contributor to the large difference in thermal pain sensitivity between the groups in this report because the percentage of patients currently taking opiate medication was similar in all the groups (Table 1). We cannot, however, rule out the possibility that dose or duration of opiate use may play a role in the severe generalized thermal hyperalgesia seen in the subgroup of CRPS patients. The goal of many pain clinics, especially ours, is to reduce or eliminate chronic opiate use if possible. The baseline QST results may prove useful in documenting possible changes in hyperalgesia with reduction of opiate usage.

We believe that thermal QST provides useful infor-

mation regarding an individual's level of sensitivity to a very controlled and reproducible set of stimuli. The qualities of the evoked sensations have been systematically studied in control subjects (20). Cold evoked pain has been described by our patients as burning, tingling, sharp, shooting, or causing exacerbation of underlying spontaneous pain. The cold pain may be reported to be located much deeper than the skin in contact with the thermode. The exact location, quality, duration, and reproducibility of cold evoked pain at a given body site may provide useful information about possible mechanisms, such as sensitized muscle afferents, loss of A-delta inhibition (23), or central sensitization (13) that may be responsible for the thermal hyperalgesia in a given individual.

The relevance of evoked thermal pain thresholds to treatment selection and outcome is now an ongoing study in our clinic. In a double blind study of ketamine infusion for CRPS, many patients received significant relief even though cold allodynia did not show dramatic improvement in the short term (24). It is possible that cold allodynia and/or heat hyperalgesia is firmly established and may take much longer to abate as demonstrated by a patient who had dramatic relief from CRPS, but cold and heat pain thresholds took much longer to normalize (25).

At present the results of quantitative sensory testing are used to document the sensory profile of the individual patient. Supportive evidence for concomitant small fiber neuropathies, hemisensory deficits, or localized sensory dysfunctions from such things as carpal tunnel, tarsal tunnel, or radiculopathy can be obtained. These form the basis for the practical use of QST in patients to improve rational treatment selection. We have also used repeated QST to document the lack of progressive subtle subclinical sensory loss in a small group of patients who received low dose thalidomide for a long period of time (unpublished results) as treatment for their CRPS (27).

It is hoped that the results of this study, which indicates there may be distinct subgroups of CRPS patients with respect to thermal hyperalgesia, will ultimately be useful in the clinic as well as in research. As information is collected on the efficacy of new individualized treatments for each patient, the correlation with thermal pain profile may prove to be a useful predictor of response.

Conclusions

In summary, thermal QST can provide useful information about an individual's sensory phenotype. The results presented here indicate that patients with CRPS can generally be categorized into specific subgroups with regards to thermal evoked pain. One group, comprising 40% of the patients, shows evidence of both cold allodynia and heat hyperalgesia, another group comprising 39% of the patients, displays neither cold allodynia nor heat hyperalgesia. A third group, comprising 14% of the patients has evidence of cold allodynia with no evidence of heat hyperalgesia, and the fourth group comprising only 7%, demonstrates heat hyperalgesia with no evidence of cold allodynia. At present we are hopeful that we may be able to determine if correlations exist between sensory phenotypes, cytokine profiles (26), and response to treatments.

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