ORIGINAL ARTICLE

Painless Electrodiagnostic Current Perception Threshold and Pain Tolerance Threshold Values in CRPS Subjects and Healthy Controls: A Multicenter Study

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■ **Abstract:** The purpose of this study is to evaluate both painless and painful sensory transmission in patients with Complex Regional Pain Syndrome (CRPS) using the automated electrodiagnostic sensory Nerve Conduction Threshold (sNCT) test. This test generates reliable, painless Current Per-

ception Threshold (CPT) and atraumatic Pain Tolerance Threshold (PTT) measures. Standardized CPT and PTT measures using constant alternating current sinusoid waveform stimulus at 3 different frequencies 5 Hz, 250 Hz, and 2 kHz (Neurometer® CPT/C Neurotron, Inc. Baltimore, MD) were obtained from CRPS subjects at a distal phalange of the affected extremity and at an ipsilateral asymptomatic control site. Matched sites were tested on healthy subjects. Detection sensitivities for an abnormal PTT and CPT test were calculated based on specificity of 90% as determined from data obtained from healthy controls. A Spearman rank correlation was used to test for a significant association between presence of allodynia and an abnormal PTT or CPT at any frequency tested. Thirty-six CRPS subjects and 57 healthy controls were tested. The highest detection sensitivity of the PTT test from symptomatic test sites was 63% for the finger and 71% for the toe. PTT abnormalities were also detected, to a lesser degree, at the asymptomatic control site (41% finger control site, 16% toe control site). The highest CPT detection sensitivity at the symptomatic site was 37% for the finger site and 53% for the toe site. CPT abnormalities were also detected at the asymptomatic control site (29% finger control site, 37% toe control site). Eighty-six percent of the CRPS subjects had either a PTT or CPT abnormality at any frequency at the symptomatic site. There was a significant correlation between presence of allodynia and presence of an abnormal CPT and PTT, respectively ($P < .01$). The correlation coefficient was lower for CPT than for PTT, ie, 0.34 versus 0.6 for the finger and 0.48 versus 0.67 for the toe, respectively. In studied CRPS patients an abnormal PTT was detected with higher sensitivity than an abnormal CPT. Assessing PTT may become a useful electrodiagnostic quantitative sensory test for diagnosing and following the course of neuropathic pain conditions. ■

Complex Regional Pain Syndrome (CRPS) is a neuropathic pain condition characterized by sensory, motor, and autonomic dysfunction. The classic presentation of CRPS includes spontaneous pain or allodynia/hyperalgesia, vasomotor or sudomotor abnormalities, usually in a distal extremity nondermatomal distribution.[1] The pain is often characterized as a burning spontaneous pain felt deeply inside the distal part of the affected extremity.[2] Motor symptoms and signs such as weakness, tremor, and dystonia are also found in many patients.[3] Trophic skin changes can be present as well.[4] The pathogenesis of CRPS remains unclear and the exact incidence is unknown. Dysfunction of the sympathetic nervous system, central and peripheral nervous system, and/or neurogenic inflammation have been hypothesized as the underlying pathophysiology.[5]

Early detection, correct diagnosis, and immediate intervention are thought to produce better outcomes. There are no specific diagnostic tests for CRPS. The diagnosis of CRPS is made on clinical grounds, based on a number of criteria including clinical signs and symptoms. Laboratory tests, including tests of autonomic instability or somatosensory disturbances, are also used to assist in the diagnosis of neuropathic pain.[6,7] Radiologic techniques (3-phase bone scan and plain X-rays) are primarily useful in the early stages of the disease.[8,9] Sensory Nerve Conduction Velocity (sNCV) tests of peripheral nerve segments have generally been found to be insensitive for detecting sensory abnormalities in CRPS patients.[5]

A sensitive, reliable, and quantitative test of pain and nonpain sensory nerve conduction may be extremely useful for diagnosing CRPS and monitoring therapeutic outcomes. Recently, it has become possible to obtain direct quantitative measurements of peripheral sensory nerve function using the electrodiagnostic sNCT(TM) test performed by the Neurometer® CPT/C device. The sNCT evaluation obtains reliable CPT and PTT measures of sensory function from the peripheral nerve to the central nervous system.[10–12] This test reportedly achieves differential neuro-excitatory effects by using different frequencies of an electrical sine wave stimulus. Biophysical considerations and indirect evidence suggest that the 2000 Hz stimulus measures reflect primarily large myelinated fiber activation, and the 5 Hz stimulus measures primarily reflect small unmyelinated fiber activation.[10–15] The ability to differentially detect increased sensitivity to stimuli (hyperesthesia) and decreased sensitivity to stimuli (hypoesthesia) enhances the sensitivity of the sNCT test over other electrodiagnostic tests such as the sNCV test. The sNCV test is only capable of evaluating large fiber conduction within a segment of a peripheral nerve and cannot quantify hyperesthesia.

In a healthy subject, the PTT has a much higher current intensity threshold than the CPT. The reliability of the PTT measure has been established in several recent studies.[16–19] Recently, PTT and CPT measures have been used to evaluate allodynia in a preliminary study of RSD patients.[20] A PTT that is abnormally low would be an expected finding consistent with the presence of allodynia in CRPS patients. Several researchers have observed that in subjects with chronic pain, electrically evoked painless sensory and pain thresholds converge.[20,21] The present multicenter study was performed to characterize CPT and PTT values from CRPS subjects and healthy controls.

MATERIALS AND METHODS

After obtaining Institutional Review Board approval and informed consent, subjects with CRPS and healthy controls were enrolled in the study. All subjects were at least 18 years of age.

CRPS Subject Inclusion Criteria

CRPS Type I or II subject inclusion criteria were adapted from those outlined by Stanton Hicks et al:[1]

1. A pain syndrome that develops after a nonpsychological initiating event or identifiable nerve injury.
2. Pain including symptoms of allodynia/hyperalgesia in the distal part of the extremity (including the distal phalanges) that is disproportionate to the inciting event.
3. Evoked dynamic or static mechanical allodynia or cold allodynia at the impaired site to be tested. Dynamic mechanical allodynia is defined as a painful response to light stroking of the skin with a cotton swab. Static allodynia is defined as a painful response to gentle continuous pressure on the skin with a blunt object, eg, a cotton swab. Cold allodynia is defined as a painful response to the evaporation of alcohol placed on the skin.
4. Concurrent or previous clinical evidence of edema, skin blood flow abnormality or abnormal sudomotor activity in the region of the pain since the inciting event.
5. No new medications effecting pain or nerve function administered within 7 days prior to the study.
6. No major psychiatric disorders.
7. No conditions that would otherwise account for the degree of pain dysfunction. Any subjects with local conditions (eg, ankle sprain, history of carpal tunnel release), ipsilateral conditions (eg, ischemia, thrombophlebitis, infection) and or systemic conditions (eg, peripheral neuropathy, diabetes, alcoholism, AIDS, Raynaud's phenomena, collagen vascular disease) were excluded from the study. Subjects with a history of neuroablative procedures or neurolytic blocks were excluded. Also subjects with sympathetic blocks within the previous 1 week were excluded.
8. No open lesions, scar tissue, or acute injury in the area of pain to be tested.

Control Subject Inclusion Criteria

Healthy, with no present or past history of neurologic disease or any condition that could affect sensory nerve function.

Testing Procedures

The automated sNCT evaluations were administered to determine the CPT measures followed by the PTT measures at standardized cutaneous test sites.[2,3] The automated sNCT methodology prevented the subject and operator from being aware of the device output parameters during testing.

The symptomatic site tested was the distal phalange of the ring finger (median, ulnar nerves, C7/C8) or great toe (superficial peroneal, deep peroneal nerves, L4/L5) on the extremity of maximal symptomatology. The intrasubject control site was the asymptomatic ipsilateral great toe or ring finger. The sites tested on the control subjects were the right ring finger and right great toe (Figure 1).

All testing was performed with subjects in stationary positions (sitting or supine) to reduce the possibility of postural compression of the nerves being tested. The study was conducted in a quiet room. sNCT testing was performed to obtain both CPT and PTT measures using the Neurometer® CPT/C electrodiagnostic device (Neurotron, Inc. Baltimore, MD) (Figure 2). The following is a brief description of the procedure. The device was situated with the controls placed out of view of the subject. The examination procedure was explained to the subject using a standardized script. The prescribed skin sites to be evaluated were examined to confirm that they were free of any signs of recent trauma, which could distort the measures. The skin was prepared for testing using a skin prep-paste. A pair of 1 cm. diameter gold electrodes separated by a 1.7 cm Mylar spreader were coated with a thin layer of chloride free electroconductive gel and then taped to the test site.

The CPT measure represents the minimal amount of a painless transcutaneous electrical stimulus required to reproducibly evoke a sensation. These measures were obtained using similar psychophysical principles as those that are used in other standardized tests of sensation such as audiometry. An automated double-blinded forced-choice testing procedure determines CPT measures to within $\pm 20\mu$Amperes. This test has been used to document sensory dysfunction including abnormally low CPT measures (hyperesthesia) as well as elevated CPT

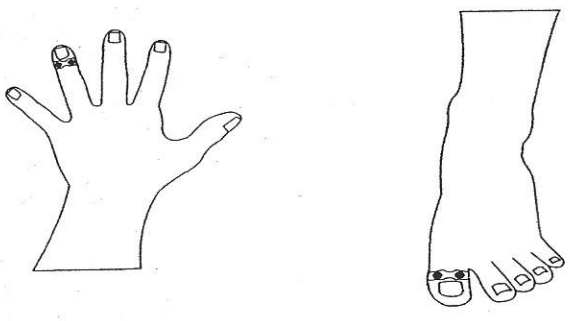

Figure 1. Test sites. Ring finger and Great toe (Neurotron, Inc., with permission).

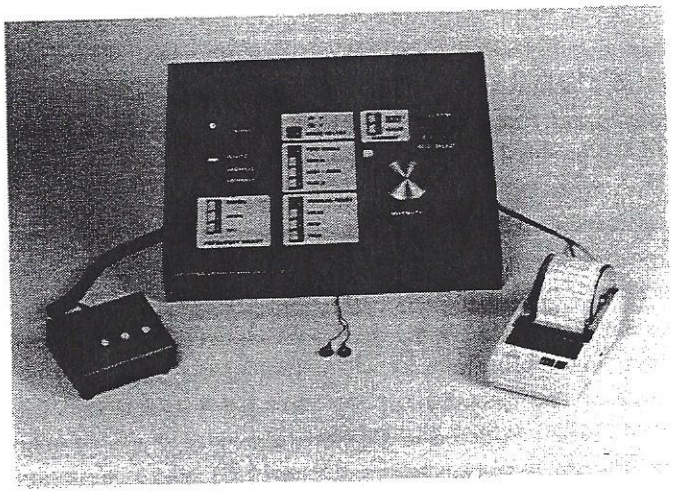

Figure 2. Photo of Neurometer® CPT/C device (Neurotron, Inc., with permission.)

measures (hypoesthesia).[11–13,24,25] The CPT determination began with the "Intensity Alignment Mode." The alternating constant current stimulus intensity was increased from zero to a maximum of 9.99 mAmperes until the subject reported detecting a sensation at the site of the electrodes. The stimulus was then turned off and represented at decreasing intensities until it was not detected, with a range of ± 0.05 mAmperes. Next, an "Automated Forced Choice CPT Determination Mode" was conducted to determine the actual CPT measures. The subject was presented with a series of forced choice tests, which consisted of randomly generated pairs of real and false (placebo) stimuli presented as a "Test A" and a "Test B" separated by a "Rest" period. A remote box with buttons paired with indicator lights labeled "Test Cycle," "Test A," "Rest/None," and "Test B" was used for each test period. A different audible tone was emitted and the corresponding button indicator light was illuminated for each test period. The subject was told to indicate, by pressing the corresponding button, when they detected stimulation at the site of the electrodes during "Test A" or "Test B." If no stimulus was detected or if they were unable to discern any difference between the test cycles, the subject was told to press the "Rest/None" button. Based on their response, the sNCT device automatically adjusted the output level of the stimulus and randomly generated a new testing order for the next pair of tests in the series. Randomly placed double-false tests were presented to assist in monitoring subject responses for consistency and accuracy. The CPT determined was defined as the average of the minimum intensity of the stimulus consistently detected and the stimulus 40 μAmperes lower that was consistently not detected. The double-blinded forced-choice paradigm ensures that the likelihood of a subject producing a measure by random chance is less than 6 chances in a 1000 ($P < .006$). This testing sequence was repeated for each of the 3 frequencies (2000 Hz, 250 Hz, 5 Hz) before moving onto the next body site. The duration of the presentation of each test and rest period was a function of the stimulus frequency: 1.65 s at 2000 Hz, 1.65 s at 250 Hz, and 2.68 s at 5 Hz.

The PTT measure represents the maximum amount of electrical stimulus that can be tolerated. The PTT test uses the same stimulus (as is used to obtain the CPT measure) to evoke aversive sensations. The PTT evaluation is noninvasive. The test is also atraumatic in that it does not cause tissue damage which enhances it's clinical utility for routine clinical use. PTT's were obtained using a self-administered standardized automated double-blinded methodology.[11,26] To initially familiarize the subject with the procedure, the test was performed on a body site not involved in the study (for the CRPS subjects this site was contralateral to the intra subject control site and for the control subjects this was the left ring finger). This PTT procedure was then performed at the same sites where the CPT values were determined. PTT measurements at the test sites were performed only once at each frequency. The stimulus was presented in an ascending "staircase" fashion. The PTT evaluation was performed by the subject pressing and holding the "Test Cycle" button on the remote box. The subject released the button to automatically discontinue the stimulus when it could no longer be tolerated. The stimulation would automatically stop if the maximum output intensity (9.99 mAmperes) was reached. The duration of each test step was a function of the stimulus frequency: 0.72 s at 2000 Hz (20 steps), 2.16 s at 250 Hz (20 steps) and 2.52 s at 5 Hz (29 steps).[26]

Evaluation of Data

CPT abnormalities are distributed in a two-sided distribution (ie, hyperesthetic or hypoesthetic). Therefore, the 5th and 95th percentile confidence intervals from control subject CPT values were determined to establish normative CPT values for finger and toe sties. Hypoesthesia was defined as a CPT greater than the 95th percentile. Hyperesthesia was defined as a CPT less than the 5th percentile. Based on the control subjects 5th and/or 95th percentile, detection sensitivities were calculated as the percentage of the CRPS subjects that had abnormal CPT values (either/or hyperesthetic or hypoesthetic, respectively).

PTT abnormalities, however, were distributed in a one-sided distribution (abnormally low), therefore the 10th percentile confidence interval was used. Based on the control subjects 10th percentile, detection sensitivities were calculated as the percentage of the CRPS subjects that had abnormally low PTT values (<10th percentile). The 10th percentile was chosen for the PTT test so that both measures (PTT and CPT) would be determined at the same specificity (90%).

The percentage of CRPS subjects who had an abnormal PTT and a normal CPT at the same symptomatic site and at the same frequency was determined. The percentage of CRPS subjects who had a normal PTT and abnormal CPT at the same symptomatic site and at the same frequency was determined. The percentage of patients who had an abnormal PTT or CPT for at least 1 of the 3 tested frequencies was calculated and expressed as combined sensitivity. However, since the specificity for testing each of the 3 frequencies was 90%, assessing the combined sensitivity may result in a specificity ranging between 70% and 90%.

The Wilcoxon Signed Rank test with Bonferroni correction was used to test for a significant difference between PTT values determined in CRPS subjects (symptomatic or control site) and healthy controls. A *P*-value of .05 was considered statistically significant. This test was not performed on the CPT data. A statistical test assessing the difference between the means was not appropriate because abnormal results could be both, below the 5% or above the 95%. Spearman rank correlation was used to test for a significant association between presence of allodynia (from the symptomatic site) and the PTT and CPT, respectively. Spearman rank correlation was used to test for a significant association between presence of allodynia and presence of an abnormal PTT or CPT at any tested frequency. A *P*-value of .05 was considered statistically significant (SigmaStat version 1, Jandel Corporation).

RESULTS

Thirty-six CRPS subjects and 57 controls were tested (Table 1). The CRPS subjects had neuropathic pain of longstanding duration (27>24 months, 3>12 months, 3>6 months, 2>3 months, 1 unknown). CPT and PTT testing were well tolerated by the CRPS and control subjects.

The difference between the PTT values for the CRPS subjects from the symptomatic site and the asymptomatic control site and the healthy controls was statistically significant ($P < .05$). The PTT was consistently more sensitive than the CPT for detection of abnormalities in CRPS subjects. Detection sensitivity and confidence interval values for abnormal PTTs are presented in Tables 2–5. The highest detection sensitivity of the PTT test was 71% (2000 Hz) when the toe was the symptomatic site and 63% (5 Hz) when the finger was the symptomatic site (Tables 2 and 3). PTT abnormalities were also detected at the asymptomatic control site (Tables 4 and 5).

Detection sensitivity and confidence interval values for abnormal CPTs (hyperesthetic and hypoesthetic) at the symptomatic and control sites are presented in Ta-

Table 1. Demographics of the CRPS subjects and healthy control subjects

	CRPS Subjects	Healthy Controls
n =	36	57
Finger symptomatic site	19	57
Toe symptomatic site	17	57
Mean age (S.D.)	45 (12)	38 (12)
Female	27	36
Male	9	21
VAS (median)	7	—
Static mechanical allodynia at symptomatic site	28	—
Dynamic mechanical allodynia at symptomatic site	29	—
Cold allodynia at symptomatic site	23	—
Allodynia of unknown type	3	—

Table 2. CRPS Subject CPT and PTT Data from Symptomatic Site Finger

	PTT*			CPT*		
ID#	2kHz	250Hz	5Hz	2kHz	250Hz	5Hz
1	***475***	450	180	288	117	42
2	675	400	840	301	110	***119***
3	***225***	***120***	***45***	277	79	62
4	825	250	***160***	173	65	27
5	***425***	250	225	144	81	39
6	925	250	***75***	209	56	18
7	***225***	***50***	***75***	***111***	***6***	***9***
8	999	710	325	224	115	***116***
9	***275***	***160***	***160***	225	116	***122***
10	825	250	***140***	251	76	38
11	***425***	***120***	***110***	223	100	63
12	***525***	***120***	***45***	190	***16***	***8***
13	999	400	350	226	89	44
14	***275***	***120***	***105***	262	119	***99***
15	625	300	***90***	***452***	73	45
16	725	***160***	***57***	***374***	71	18
17	775	300	180	227	***133***	27
18	***225***	***25***	***30***	***12***	***10***	***9***
19	575	250	250	262	69	26
POSITIVE	9	8	12	4	4	7
SENSITIVITY	0.47	0.42	0.63	0.21	0.21	0.37
10th-%	575	200	178			
5th-%				130	30	10
95th-%				318	120	79

* = Values are in CPT units (1 unit = 10 μAmperes). Statistically significant values are bolded.

Table 3. CRPS Subject CPT and PTT Data from Symptomatic Site Toe

	PTT*			CPT*		
ID#	2kHz	250Hz	5Hz	2kHz	250Hz	5Hz
1	999	920	650	***817***	***438***	***264***
2	***425***	***250***	***140***	***23***	***31***	***9***
3	***475***	300	300	440	***228***	122
4	***325***	***120***	275	277	121	51
5	675	300	***105***	193	179	44
6	***425***	***200***	***140***	***201***	87	57
7	***325***	***80***	***30***	***207***	***24***	***3***
8	***575***	***200***	400	355	165	***164***
9	775	350	***140***	***94***	***26***	***12***
10	***325***	***160***	***160***	256	63	48
11	***475***	***250***	***120***	400	154	42
12	***425***	***200***	***105***	***189***	84	48
13	***225***	***80***	***75***	***191***	116	35
14	999	510	650	371	78	23
15	***425***	***160***	***105***	250	***28***	***12***
16	***625***	***250***	275	***12***	***32***	***8***
17	999	350	275	***848***	***440***	***257***
POSITIVE	12	11	10	9	8	8
SENSITIVITY	0.71	0.65	0.59	0.53	0.47	0.47
10th-%	655	300	200			
5th-%				192	58	22
95th-%				433	197	123

* = Values are in CPT units (1 unit = 10 μAmperes). Statistically significant values are bolded.

Table 4. CRPS Subject CPT and PTT Data from Control Site Finger

	PTT*			CPT*		
ID#	2kHz	250Hz	5Hz	2kHz	250Hz	5Hz
1	999	840	710	210	86	48
2	999	510	840	218	81	57
3	999	510	450	***324***	***142***	72
4	***375***	***160***	225	239	88	31
5	675	250	200	288	101	***90***
6	***275***	***80***	***30***	207	***26***	10
7	999	450	450	259	92	20
8	575	250	250	149	75	***95***
9	575	200	***120***	172	49	23
10	***375***	***120***	***75***	205	42	32
11	575	200	180	247	111	76
12	***475***	***160***	***120***	183	62	19
13	775	***50***	***30***	***80***	***10***	***7***
14	725	300	450	149	34	10
15	999	***120***	275	***529***	***167***	***97***
16	***375***	***160***	***75***	***126***	***15***	***4***
17	575	300	180	226	34	39
POSITIVE	5	7	6	4	5	5
SENSITIVITY	0.29	0.41	0.35	0.24	0.29	0.29
10th-%	575	200	178			
5th-%				130	30	10
95th-%				318	120	79

* = Values are in CPT units (1 unit = 10 μAmperes). Statistically significant values are bolded.

bles 2–5. The highest CPT detection sensitivity was 53% (2000 Hz) when the toe was the symptomatic site and the highest detection sensitivity of the CPT test was 37% (5 Hz) when the finger was the symptomatic site (Tables 2 and 3). CPT abnormalities were also detected at the asymptomatic control site (Tables 4 and 5).

There was a significant correlation between presence of allodynia and presence of an abnormal CPT and PTT, respectively ($P < .01$). The correlation coefficient was lower for CPT than for PTT, ie, 0.34 versus 0.6 for the finger and 0.48 versus 0.67 for the toe, respectively.

Sixty-four percent of the CRPS subjects had an abnormal PTT value with a normal CPT value at the same symptomatic site at the same frequency. Conversely, 33% of the CRPS subjects had an abnormal CPT value with a normal PTT value at the same symptomatic site at the same frequency. Eighty-six percent of the CRPS subjects had either a PTT or CPT abnormality at any frequency at the symptomatic site.

DISCUSSION

The lack of a reliable sensitive test for assessing sensory and nociceptive neuronal processing in CRPS patients has been a hindrance in the accurate diagnosis and evaluation of treatment outcome. The result of this study suggests that assessment of PTT, and to a lesser degree CPT, may become a useful test in the evaluation of CRPS patients.

Allodynia correlated significantly with an abnormal PTT and to a lesser degree with an abnormal CPT. Abnormal PTT values were detected with greater frequency at the toe (59%–71% for different frequencies) than at the finger (42%–63%). The detection sensitivity for an abnormal PTT was greater than the detection sensitivity for an abnormal CPT.

The detection of PTT and CPT abnormalities among the CRPS subjects, at the symptomatic site and the asymptomatic site was consistent with earlier work demonstrating abnormal sensory processing of noxious and nonnoxious stimulation at symptomatic and asymptomatic sites.[21,27] Furthermore, previous research has shown central nervous system dysfunction or pathology in CRPS subjects.[28] Other researchers have also shown that sensory deficits frequently extend, ipsilaterally, proximal to the painful area of the affected extremity.[29] A percentage of the CRPS subjects had abnormal PTT values with normal CPT values at the same site suggesting peripheral sensory nerve function was normal in these subjects. Also, some of the CRPS subjects had normal PTT values and abnormal CPT values at the same site suggesting peripheral nerve function was abnormal in these subjects. Together these findings suggest that the

Table 5. CRPS Subject CPT and PTT Data from Control Site Toe

	PTT*			CPT*		
ID#	2kHz	250Hz	5Hz	2kHz	250Hz	5Hz
1	999	760	250	406	158	112
2	999	650	760	***441***	***214***	***167***
3	***525***	***250***	***160***	***450***	***202***	101
4	999	350	204	288	86	***18***
5	999	710	570	328	145	77
6	725	400	300	236	101	41
7	***575***	***250***	***180***	***149***	79	37
8	825	400	350	333	***214***	***139***
9	925	400	650	375	130	71
10	999	350	200	374	152	32
11	***275***	***120***	***38***	225	102	40
12	875	400	275	266	126	80
13	999	570	650	***520***	***218***	114
14	999	510	225	***534***	***274***	***142***
15	825	510	250	421	111	55
16	925	350	204	***552***	196	59
17	999	650	510	***516***	***478***	***220***
18	999	400	200	356	147	78
19	875	300	450	364	188	44
POSITIVE	3	3	3	7	6	5
SENSITIVITY	0.16	0.16	0.16	0.37	0.32	0.26
10th-%	655	300	200			
5th-%				192	58	22
95th-%				433	197	123

* = Values are in CPT units (1 unit = 10 μAmperes). Statistically significant values are bolded.

pathophysiology of CRPS involves both the central and peripheral mechanisms.

Some CRPS patients had a normal CPT but an abnormal PTT or vice versa. The finding of an abnormal PTT but a normal CPT is expected since this study documented a higher detection sensitivity for an abnormal PTT compared with an abnormal CPT in CRPS subjects with allodynia. The finding of an abnormal CPT but normal PTT was generally made in patients presenting with signs of neurological deficiency, ie, hypoesthesia (abnormally high CPT). Taken together these findings suggest that nociceptive and nonnociceptive neuronal transmission could have been affected differentially in studied CRPS subjects. It is interesting that patients presenting with hyperesthesia consistently had an increased sensitivity to noxious stimulation but patients presenting with hypoesthesia had not. An alternative explanation for these findings could be that PTTs and CPTs were affected differentially by medications taken by CRPS subjects. Opiates are known to affect PTT values, in healthy subjects, independent of CPT measures at the same site (for 250 Hz and 5 Hz measures).[19] Neuraxial, intravenous and topical lidocaine have been shown to affect CPT measures (preferentially 5 Hz) in healthy subjects and those with neuropathic pain.[30–34]

CONCLUSION

This study of CRPS subjects demonstrated that an abnormal PTT was detected with higher sensitivity than an abnormal CPT. Assessing the PTT may become a useful electrodiagnostic clinical test for diagnosing and following the course of neuropathic pain conditions. Future research is needed to determine if this methodology can document improvement of measures that correlate with clinical improvement and if initial measures are predictive of specific treatment response rates.

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