Complex Regional Pain Syndromes in Children and Adolescents

Regional and Systemic Signs and Symptoms and Hemodynamic Response to Tilt Table Testing

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Objective: Complex regional pain syndromes (CRPS) involve neuropathic limb pain and localized circulatory abnormalities. The authors hypothesized that (1) pediatric CRPS patients exhibit systemic autonomic symptoms and orthostatic and/or cardiac sympatho-vagal dysregulation and (2) their orthostatic regulation differs from healthy controls and pediatric patients with postural orthostatic tachycardia syndrome (POTS).

Methods: CRPS children and adolescents (n = 20) underwent a 6-week trial of physical therapy and cognitive-behavioral treatment. Measures included pain and function scores, regional and systemic autonomic symptom profiles, heart rate and blood pressure with tilt, heart rate variability indices, and baroreflex gain. Systemic autonomic symptoms were recorded in 55 healthy pediatric controls. Tilt responses in CRPS patients were compared with those of 21 POTS patients and 39 healthy controls.

Results: CRPS patients' regional autonomic symptoms, pain, and limb function improved over 6 weeks ($P < 0.01$). At baseline CRPS patients reported more systemic autonomic symptoms than controls ($P < 0.05$). Tilt table test showed orthostatic stability, but the mean heart rate increase with tilt was greater in CRPS patients than controls ($P < 0.001$). POTS patients showed significant increases with tilt in mean heart rate and diastolic and systolic blood pressures compared with controls ($P < 0.001$). There were significant increases in the mean systolic and diastolic blood pressures in POTS compared with CRPS patients but no difference in the mean heart rate between groups.

Discussion: CRPS patients reported multiple regional and systemic autonomic symptoms that improved during the study course, and they experienced minimal and transient tilt table-induced hemodynamic changes compared with POTS patients but relatively similar to controls.

Key Words: neuropathic pain, complex regional pain syndrome, tilt table test, autonomic signs and symptoms, postural orthostatic tachycardia syndrome

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Complex regional pain syndromes (CRPS) type 1 (CRPS1, also known as reflex sympathetic dystrophy) and type 2 (CRPS2, also known as causalgia) are neuropathic pain conditions increasingly recognized in children and adolescents.[1–4] Patients frequently report regional and also systemic autonomic symptoms. Although many adolescents exhibit occasional dizziness or near-syncope with orthostatic or emotional stressors, most have good orthostatic tolerance.[5] Some children and adolescents show exaggerated responses to orthostatic stress, including dizziness and postural tachycardia. Postural orthostatic tachycardia syndrome (POTS) has been recognized increasingly among children and adolescents in recent years, though no population-based estimates of incidence or prevalence are available. POTS is characterized by symptoms of orthostatic intolerance associated with an excessive increase in heart rate (HR) on orthostatic challenge.[6]

It is therefore relevant to ask whether the apparent *regional* autonomic dysfunction in CRPS could be a manifestation of impaired *systemic* autonomic function, and whether responses to orthostatic stress in CRPS patients differ from healthy controls or children and adolescents with POTS. We hypothesized that (1) pediatric CRPS patients exhibit systemic autonomic

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symptoms, signs of hemodynamic instability with orthostatic challenge, and/or abnormal HR variability, and (2) their responses to tilt table testing differ from healthy controls and from pediatric patients with POTS.

METHODS

Protocols were approved by the Committee on Clinical Investigation at Children's Hospital, Boston, and at the University Medical Center Utrecht, The Netherlands. Written informed parental consent and patient assent were obtained. Children and adolescents with CRPS based on revised IASP taxonomy[7] were recruited as part of a prospective 6-week trial of physical therapy and cognitive-behavioral treatment as reported previously.[3] Inclusion criteria were newly diagnosed CRPS affecting one extremity. Two thirds (n = 13) of our patients developed CRPS after a definable injury or surgery. Standardized assessments were performed at enrollment, after the 6-week treatment (short-term follow-up), and at 6-month (long-term) follow-up. These included pain and function scores, gait measures, regional and systemic sign and symptom profiles, quantitative sensory testing, psychological inventories, and tilt table testing. A separate school-based cohort of healthy children and adolescents who participated in a study of normal sensory thresholds in children[8] completed a standardized systemic autonomic symptom profile, as detailed below. Hemodynamic response to tilt table testing at the first assessment was compared with healthy controls and a group of POTS patients referred to the Cardiology Clinic at Children's Hospital with recurrent episodes of syncope or near-syncope.

CRPS Patients

Twenty adolescents were studied (19 girls, 1 boy; mean age 13.1 ± 2.5 years). In all children, the lower extremity was affected: the foot and ankle in 14 children, knee in 5, and lower leg in 1. The median duration of the pain was 2 months before enrollment.

Healthy Control Population for the Systemic Symptom Profile

Fifty-five children and adolescents were evaluated (52 girls, 3 boys; mean age 11.3 ± 3.1 years). They were recruited from a nearby school and matched by age and sex to the CRPS group. All were healthy and none reported any regional symptoms, regional signs, or spontaneous pain.

Healthy Control Population for the Hemodynamic Parameters of the Tilt Table Test

Thirty-nine subjects (24 girls, 15 boys, mean age 11.7 ± 2.7 years) were studied at the Academic Department, General Pediatrics, University Medical Center Utrecht, The Netherlands. They were recruited from primary and high schools in the city and region of Utrecht, The Netherlands.

Patient Population With POTS

Twenty-one adolescents (13 girls, 8 boys, mean age 15.5 ± 2.2 years) were studied. POTS patients were referred to the pediatric cardiology clinic for recurrent near-syncopal or syncopal symptoms and subsequently evaluated with a tilt table test. They reported multiple long-standing symptoms (median duration 12 months, mean 18 ± 16 months).

Regional Physical Signs and Symptoms in the Affected Extremity

Two physicians (P.M.M., N.F.S.) prospectively performed structured examinations of the CRPS patients' affected extremities before and after treatment and at the 6-month follow-up. A 10-item patient self-report regional symptom questionnaire and a 10-item physician's examination for regional physical signs were documented in accordance with the standard diagnostic features of CRPS.[7] In addition, the authors conducted nerve mapping of the pain distribution in the affected limb, visual analog scale (VAS) ratings for brush allodynia, pinprick hyperalgesia, and summation to pinprick in the hyperalgesic area, as described in our previous study.[9] Temperature differences of more than 3°C between the affected and unaffected limbs were regarded as clinically significant. Differences in thigh or calf circumference were measured at standardized sites above and below the knee, and a discrepancy of more than 2 cm was scored as muscle atrophy.

Pain, Function, and Regional Autonomic Symptom and Sign Scores

Self-report of pain at rest was assessed with the mechanical color VAS.[10] Limb function was assessed with a global function score[2] ranging from 0 to 5 (wheelchair-bound, 0; non-weight-bearing on crutches, 1; use of a cane with partial weight-bearing, 2; unrestricted walking with a limp, 3; normal walking with partial but restricted participation in aerobic sport activities, 4; and vigorous exercise without any restriction, 5).

Systemic Autonomic Symptom Profile

A structured interview[11] tabulated systemic autonomic symptoms. Interviews were conducted once for school-based healthy controls and on three occasions for CRPS patients: at enrollment, after the 6-week treatment protocol, and at the 6-month follow-up. The POTS patients were not interviewed for the systemic autonomic symptom profile.

Orthostatic symptom subscores (OSS) were rated from 0 to 4 (no symptoms at all, 0; rare or occasional [monthly] dizziness without associated symptoms, 1; frequent [weekly or daily] dizziness without any associated symptoms or occasional dizziness with at least one associated symptom, 2; frequent orthostatic symptoms with near-syncope or occasional syncope, 3; frequent syncope, 4). Associated symptoms included palpitations, blurred vision, anxiety, nausea, weakness, pallor, vertigo, tremulousness, and clammy skin. Aggravating factors

were noted, including worsening after eating, early in the morning, with prolonged standing, or with exertion/walking.

Tilt Table Test

We used the modified 60-degree head-up tilt protocol described previously.[12] CRPS patients completed the tilt protocol at enrollment, after the 6-week treatment protocol, and at the 6-month follow-up. Normal controls and POTS patients had the same initial portion of the 12-minute tilt protocol as CRPS patients with spontaneous respiration. Lead 2 of a three-lead surface ECG and oscillometric blood pressure (Dinamap) on the right upper arm every 2 to 3 minutes were recorded on an HP monitor model 68. Continuous noninvasive arterial blood pressure was recorded with a finger photoplethysmograph (Finapress, Ohmeda 2300). Beat-to-beat variability in heart rate (HRV) and systolic and diastolic blood pressure (BP) were assessed during a 6-minute session of spontaneous breathing. After completion of the standard tilt protocol used for all three groups, CRPS patients also completed tilt protocols with a 4-minute fixed-rate interval breathing (15 breaths/min, 0.25 Hz) and a 6-minute irregular (random) breathing interval, in an attempt to further evoke subtle patterns of cardiac autonomic dysfunction.[13]

Tilt tests were aborted if there was syncope, marked near-syncopal symptoms, significant relative bradycardia, or significant orthostatic hypotension. Significant orthostatic hypotension during tilt was defined as a drop in systolic blood pressure of more than 30 mm Hg. Significant relative bradycardia was defined as a HR below 75% of the resting HR during tilt. Near-syncope was defined as significant hypotension with or without a significant relative bradycardia but without loss of postural tone, whereas syncope was defined as significant hypotension with or without a significant relative bradycardia accompanied by loss of postural tone and loss of consciousness. POTS was diagnosed by symptoms of orthostatic intolerance and with more stringent inclusion criteria of an increase in sinus HR of more than 40 bpm or to a rate of more than 120 bpm during the first 6 minutes of tilt, because of the increased orthostatic intolerance observed in otherwise healthy adolescents.[5,7,14–16]

Power spectral estimates of HR variability were quantified using the integral of the spectrum in a low-frequency region (LF, 0.02–0.15 Hz) and a high-frequency region (HF, 0.15–0.5 Hz), as well as by the ratio of LF to HF power (LF/HF), an index of sympathovagal balance.[17] Measurements of LF and HF power were made in absolute values of power ($msec^2$). Normalized units (nu) represent the relative value of each power component in proportion to the total power minus the very-low-frequency (VLF < 0.02 Hz) component.[18]

Baroreflex gain was calculated using the mean and SD of the alpha coefficient.[19] It was calculated as the square root of the power spectrum of the RR interval divided by the corresponding power spectrum of the systolic noninvasive continuous blood pressure for the LF band and HF band separately.

Statistical Analysis

Differences in continuous variables over time were assessed with the Greenhouse-Geisser F-test in repeated-measures analysis of variance (ANOVA) and paired *t* tests for comparing supine and tilt positions.[20] For spontaneous breathing, differences in HR and systolic and diastolic BP were compared between CRPS, POTS, and controls using factorial ANOVA.[21] Because pain and function scores did not follow a normal distribution, medians are presented and differences over time were evaluated by the Wilcoxon signed-ranks test. Changes in sensory, motor, and autonomic characteristics were assessed using the McNemar test.[22] Proportions of CRPS patients who reported headache, fainting, vasomotor, and secretomotor and gastrointestinal symptoms were compared with controls using the Fisher exact test, and OSS scores by the Mann-Whitney test. *P* values are all two-tailed with a Bonferroni adjustment used where appropriate. Statistical analysis was performed using the SPSS package (version 12.0, SPSS Inc, Chicago, IL). Power analysis indicated that sample sizes of 20 patients with CRPS, 20 with POTS, and 50 controls would provide 80% power to detect a difference of 1 SD in hemodynamic variables and a 10% difference in the frequency of symptoms between groups (nQuery Advisor, version 5.0, Statistical Solutions, Saugus, MA). To provide a measure of variability, 95% confidence intervals were determined using Pratt's normal approximation.[23]

RESULTS

Self-Reported Regional Symptoms and Regional Physical Signs in CRPS Patients

Both regional symptoms (Table 1) and regional physical signs (Table 2) were common in the CRPS patients at baseline (pretreatment) evaluations. Some but not all of these regional symptoms and signs showed significant improvements at the 6-week and 6-month follow-up assessments.

Systemic Autonomic Symptom Profiles

At baseline, CRPS patients reported significantly more frequent systemic autonomic symptoms than controls (Table 3). Eleven of the 20 patients reported orthostatic symptoms and 3 patients had an additional history of fainting episodes. At the 6-week follow-up, 16 patients continued to participate in the study. These patients reported significantly more symptoms on the systemic autonomic profile compared with controls, though at that point only 6 of 16 patients continued to report orthostatic symptoms. At the 6-month follow-up, there were no significant differences between the CRPS and control groups with respect to systemic autonomic symptom profiles and orthostatic symptoms except for fainting, which occurred at a significantly higher rate in the CRPS group ($P < 0.05$) (see Table 3). All patients

TABLE 1. Self-Reports of Regional Symptoms in CRPS

	Baseline (n = 20)	6 Weeks* (n = 16)	*P* Value, Baseline vs. 6 Weeks	6 Months† (n = 14)	*P* Value, Baseline vs. 6 Months
Sensory/Motor Symptoms					
VAS pain score	6 (0.2–10)	0.5 (0–10)	< 0.01	0 (0–4.6)	< 0.001
95% CI	0.1–10	0–10		0–4.5	
Allodynia	16 (80%)	7 (44%)	< 0.01	3 (21%)	< 0.01
95% CI	56–94%	20–70		5–50	
Dysesthesia	9 (45%)	2 (13%)	0.13	2 (14%)	0.63
95% CI	23–68	2–38		2–42	
Hyperpathia	12 (60%)	4 (25%)	< 0.05	4 (29%)	0.18
95% CI	36–80	7–52		8–58	
Hair/nail changes	2 (10%)	2 (13%)	0.99	1 (7%)	0.99
95% CI	1–32	2–38		0–33	
Muscle weakness	13 (65%)	6 (38%)	0.06	2 (14%)	0.07
95% CI	41–85	15–65		2–42	
Loss of motion	12 (60%)	2 (13%)	< 0.01	1 (7%)	< 0.01
95% CI	36–80	2–38		0–33	
Autonomic Symptoms					
Swelling	13 (65%)	5 (31%)	0.07	1 (7%)	< 0.05
95% CI	41–85	10–58		0–33	
Temperature change	18 (90%)	3 (19%)	< 0.001	2 (14%)	< 0.001
95% CI	68–98	4–45		2–42	
Discoloration	18 (90%)	8 (50%)	0.07	4 (29%)	< 0.01
95% CI	68–98	25–75		8–58	
Moisture change	7 (35%)	1 (6%)	0.22	0 (0%)	0.50
95% CI	15–59	0–30		0–23	

VAS pain score, recorded at rest, is presented as median score and range and compared by Wilcoxon signed-ranks test. Changes in other variables were assessed by the McNemar test.

*Four patients dropped out at 6-week testing, 2 because of persistent pain and hyperalgesia and 2 because of resolution of pain and unwillingness to return for testing.

†Two additional patients with resolution of pain were unwilling to return at 6 months.

with POTS by definition had dizziness or lightheadedness in addition to other symptoms of chronic orthostatic intolerance.[6]

Responses to Tilt Table Testing

Hemodynamics in CRPS Patients

In baseline assessments, HR increased significantly from 81 ± 14 bpm in the supine position to 102 ± 14 bpm with head-up tilt ($P < 0.001$). Diastolic BP increased significantly from 55 ± 9 mm Hg in the supine position to 62 ± 10 mm Hg with tilt ($P < 0.01$), whereas the systolic Blood pressure remained unchanged. These changes in HR and diastolic BP with tilt at baseline occurred consistently during all patterns of breathing and during the two 6-week and 6-month follow-up sessions.

Hemodynamic Comparisons Between CRPS Patients, POTS Patients, and Controls

In baseline assessments, mean supine values of HR and systolic BP did not significantly differ between CRPS patients, POTS patients, and controls (Table 4). Supine diastolic BP was significantly higher in the POTS patients compared with the CRPS patients ($P < 0.01$), and supine diastolic BP was not significantly different between CRPS patients and controls.

With head-up tilt, both mean systolic and diastolic BP were significantly higher in POTS patients compared with CRPS patients and controls. The mean systolic and diastolic BP did not differ between CRPS patients and controls. The HR values were not significantly different between POTS patients and CRPS patients; HR values in both of these groups were significantly higher than in controls (see Table 4).

Orthostatic Symptoms With Tilt in CRPS Patients

Two patients developed near-syncope during one of the three tilt table sessions that required cessation of the testing. The first patient, who reported a pretest OSS of 2, developed near-syncope (significant orthostatic hypotension with bradycardia) during baseline assessment. This patient was asymptomatic during the 6-week follow-up session but reported transient dizziness during the 6-month follow-up session; in both of these sessions, hemodynamic changes were inconsequential. The second patient reported a pretest OSS of 0 and had uneventful tilt table testing at baseline and the 6-month sessions, but at the 6-week follow-up session the patient reported a pretest OSS of 1 and developed near-syncope (significant orthostatic hypotension with preservation of HR).

An additional 7 of 20 patients with CRPS reported dizziness during tilt testing. Four of these seven had reported a prior history of orthostatic symptoms. Six developed dizziness during the tilt table test at baseline and one patient at the 6-week follow-up test; in all, the dizziness resolved within 2 to 5 minutes while in the tilt position. While in the tilt position, there was a minimal

TABLE 2. Physician Assessment of Regional Physical Signs in CRPS

	Baseline (n = 20)	6 Weeks* (n = 16)	*P* Value, Baseline vs. 6 Weeks	6 Months† (n = 14)	*P* Value, Baseline vs. 6 Months
Sensory/Motor Signs					
Allodynia	15 (75%)	7 (44%)	< 0.05	3 (21%)	< 0.05
95% CI	51–91	20–70		5–50	
Hyperalgesia	16 (80%)	7 (44%)	< 0.05	5 (36%)	< 0.05
95% CI	56–94	20–70		13–64	
Summation	17 (85%)	9 (56%)	0.06	7 (50%)	0.13
95% CI	62–97	30–80		23–77	
Hair/nail changes	2 (10%)	0 (0%)	1.00	0 (0%)	1.00
95% CI	1–32	0–20		0–23	
Muscle atrophy	5 (25%)	0 (0%)	0.06	0 (0%)	0.13
95% CI	9–49	0–20		0–23	
Loss of motion	11 (55%)	0 (0%)	< 0.05	0 (0%)	< 0.01
95% CI	32–77	0–20		0–23	
Function score	1 (0–3)	4 (1–5)	< 0.001	5 (1–5)	< 0.001
95% CI	0–3	1–5		1–5	
Autonomic Signs					
Swelling	5 (25%)	2 (13%)	0.69	0 (0%)	0.13
95% CI	9–49	2–38		0–23	
Temperature change	5 (25%)	0 (0%)	0.13	0 (0%)	0.13
95% CI	9–49	0–20		0–23	
Discoloration	11 (55%)	6 (38%)	0.51	0 (0%)	< 0.05
95% CI	32–77	15–65		0–23	
Moisture change	0 (0%)	0 (0%)	0.99	0 (0%)	0.99
95% CI	0–17	0–20		0–23	

Function scores are presented as median and range and compared by Wilcoxon signed-ranks tests. Changes in other signs were compared by the McNemar test.
*Four patients dropped out at 6-week testing, 2 because of persistent pain and hyperalgesia and 2 because of resolution of pain and unwillingness to return for testing.
†Two additional patients with resolution of pain were unwilling to return at 6 months.

decrease of systolic BP (from mean 111 ± 8.2 to 109 ± 5 mm Hg), a minimal increase in diastolic BP (from mean 49 ± 9 to 51 ± 8 mm Hg), and a slight increase in HR (mean 86 ± 10 to 95 ± 12 bpm) compared with the supine position. Only four of these seven patients completed all three study sessions. Two patients completed their 6-week sessions but chose not to return at 6 months because they were feeling well and saw no benefit. One patient did not comply with the physical therapy and did not return for the 6-week or 6-month follow-up visits due to excessive pain and hyperalgesia.

An additional six patients who reported a history of dizziness using the OSS had uneventful tilt testing, with stable hemodynamics and no reports of dizziness.

HRV and Baroreflex Gain With Tilt in CRPS Patients

At baseline measurement, the mean LF (reflecting both vagal and sympathetic nerve activity) was 62 ± 20 nu in the supine position and significantly increased to 84 ± 9 nu ($P < 0.001$) with the tilt position. The HF power (reflecting relative vagal dominance) was 38 ± 20

TABLE 3. Systemic Autonomic Profile for CRPS Patients and Healthy Controls

Symptoms	Baseline (n = 20)	6 Weeks (n = 16)	6 Months (n = 14)	Controls (n = 55)	*P* Value, Baseline vs. Controls	*P* Value, 6 Months vs. Controls
Headache	13 (65%)	10 (63%)	7 (50%)	18 (33%)	< 0.05	0.35
95% CI	41–85	35–85	23–77	21–47		
Fainting	3 (15%)	2 (13%)	2 (14%)	0 (0%)	< 0.05	< 0.05
95% CI	3–37	2–38	2–42	0–6		
Vasomotor	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0.27	1.00
95% CI	1–24	0–20	0–23	0–6		
Secretomotor	5 (25%)	4 (25%)	1 (7%)	1 (2%)	< 0.01	0.37
95% CI	9–49	7–52	0–33	0–10		
Gastrointestinal	9 (45%)	5 (31%)	1 (7%)	1 (2%)	< 0.001	0.37
95% CI	23–68	10–58	0–33	0–10		
OSS*	1 (0–3)	0 (0–2)	0 (0–2)	0 (0–2)	< 0.001	0.10
95% CI	0–3	0–2	0–2	0–2		

The Fisher exact test was used to compare patients and controls on all variables except OSS (Mann-Whitney test).
*Median score and range.

TABLE 4. Between-Group Comparison of Hemodynamic Responses to Tilt Testing

Hemodynamic Variable	CRPS (n = 20)	POTS (n = 21)	Controls (n = 39)	*P* Value, CRPS vs. POTS	*P* Value, CRPS vs. Controls	*P* Value, POTS vs. Controls
Systolic blood pressure (mm Hg)						
Supine	110 ± 12	112 ± 17	112 ± 13	1.00	1.00	1.00
Tilt	110 ± 10	121 ± 16	109 ± 14	0.04*	1.00	< 0.001†
Diastolic blood pressure (mm Hg)						
Supine	55 ± 9	65 ± 18	61 ± 9	0.01*	0.23	0.68
Tilt	62 ± 10	80 ± 16	59 ± 8	< 0.001†	1.00	< 0.001†
Heart rate (bpm)						
Supine	81 ± 14	75 ± 15	75 ± 10	0.33	0.27	1.00
Tilt	102 ± 14	107 ± 22	72 ± 11	0.88	< 0.001†	< 0.001†

ANOVA with Bonferroni-corrected *t* test comparisons were used to compare the differences in blood pressure and heart rate among CRPS, POTS, and controls. Statistically significant comparisons.
*$P < 0.05$.
†$P < 0.001$.

nu while supine and decreased significantly to 16 ± 9 nu with tilt ($P < 0.001$). The LF/HF ratio in the supine position was 3.0 ± 3.3 and increased to 8.0 ± 8.8 with tilt ($P < 0.01$). Similar trends were observed at the 6-week and 6-month follow-ups throughout all patterns of breathing. LF baroreflex gain remained unchanged between supine and tilt at all three study sessions. HF baroreflex gain decreased significantly during tilt position compared with supine in all three study sessions.

DISCUSSION

The major findings of this study are:

1. CRPS patients have variable regional autonomic signs and symptoms. Not all the reported subjective symptoms of sensory, motor, and autonomic abnormalities could be verified on the day of the examination. Several possibilities could explain this apparent discrepancy: (1) natural history of reduced severity of pain and autonomic dysfunction over time,[7] so that prior abnormalities may have improved before the baseline assessments, (2) spontaneous fluctuation in sympathetic arousal at times before the baseline assessments due to emotions, ambient temperature, or other factors, so that a single examination may miss these findings,[3,24] or (3) hypervigilance. In general, the abnormal regional symptoms and signs improved over time in this study (see Tables 1 and 2), as patients also showed improvement in pain and motor function.
2. CRPS patients reported frequent systemic autonomic symptoms that persisted in many patients at the 6-week evaluations, despite improvement in pain and function scores at that time, though most had resolution of systemic symptoms within 6 months (see Table 3).
3. Tilt table testing in CRPS patients showed some differences from controls, but milder hemodynamic consequences and symptoms compared with POTS patients. Despite frequent self-reported systemic symptoms, near-syncope with tilt was infrequent in CRPS patients, and no patient showed true syncope, unlike the POTS patients. The elevation in diastolic BP during tilt table testing was relatively similar in the CRPS and control groups, but the HR increase was significantly greater in the CRPS group than in controls. Moreover, the CRPS group exhibited intact quantitative indices of HR variability and baroreflex gain, and their calculated measurements are within the range of normal values reported in previous pediatric case series.[25–27] The HR and BP elevation was significantly higher in the POTS group compared with controls and may suggest abnormal autonomic regulation; however, multiple mechanisms may be consistent with these observations, and further research is needed to clarify the underlying mechanisms.[6]
4. Our findings do not support the hypothesis that pediatric CRPS patients show severe impairments in systemic cardiovascular autonomic regulation. The higher frequency of reported systemic autonomic symptoms among CRPS patients remains unexplained.

Some pediatric rheumatologists and pain physicians have chosen to lump together children and adolescents with CRPS, fibromyalgia syndrome, and other unexplained musculoskeletal painful conditions under the heading "amplified musculoskeletal pain syndrome."[28,29] Although these conditions may share the feature of persistent pain and a favorable therapeutic response to rehabilitative treatment, the clinical features and diagnostic criteria of CRPS are quite distinct from fibromyalgia syndrome or generalized musculoskeletal pain. Further study is warranted to elucidate the distinct mechanisms underlying each of these pain disorders.

There are a number of limitations to this study. There was a high rate of dropouts in the 6-week and 12-month follow-up assessments of the CRPS patients for several reasons, including resolution of pain with unwillingness to return to the hospital, persistence of pain with

consequent unwillingness to undergo further testing, inconvenience of long-distance travel to the testing site, and general difficulties in adolescents' willingness to participate in nontherapeutic clinical research protocols. Our results cannot be generalized beyond patients with short-term CRPS symptoms in one extremity only. As we did not have an untreated comparison group (ie, CRPS patients who did not receive physical therapy or cognitive-behavioral treatment), we cannot exclude the possibility that the improvement of signs and symptoms is a natural evolution over time, unrelated to rehabilitative treatment. Neither CRPS nor POTS patients were selected randomly. Because POTS patients were referred to the cardiology clinic because of the severe orthostatic symptoms, they would be expected to respond to tilt table testing with pronounced orthostatic and hemodynamic changes. Similarly, healthy control subjects were invited to participate in the study through school settings but were not recruited by a population-based random process. Two unrelated control groups were used for symptom scores and for tilt testing, in part in response to Institutional Review Board concerns about not repeating previously obtained measures in pediatric volunteer studies. The examining physicians were not blinded to each patient's presumed diagnosis. Finally, more precise and comprehensive systemic and regional autonomic measurements might have been able to detect more subtle forms of autonomic dysfunction, but they were omitted to avoid an excessive burden on children and adolescents with chronic pain.[30,31]

In conclusion, although pediatric CRPS patients reported multiple systemic autonomic symptoms and regional sensory, motor, and autonomic complaints at presentation, they exhibited relatively milder abnormalities in observable signs by physical examination and tilt table testing. In this respect, they appear different from both patients with POTS and from controls. Designs of future studies of autonomic function in CRPS patients should account for these apparent discrepancies between symptom reports and physical signs and physiologic measurements; possibly by use of repeated or remote measurements (eg, with Holter monitors) and by use of structured daily symptom diaries. Physicians should not disregard CRPS patients' complaints of regional symptoms when not present on examination by a physician on a particular day. Additional methodologies are needed to elucidate the mechanisms that underlie sensory, autonomic, and motor dysfunction in children and adolescents with CRPS.

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