

Heart Rate Variability in Complex Regional Pain Syndrome during Rest and Mental and Orthostatic Stress

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ABSTRACT

Background: Complex regional pain syndrome (CRPS) is a pain condition with regional sensory and autonomic abnormalities in the affected limb. The authors studied systemic autonomic and hemodynamic function in CRPS patients during rest, and during orthostatic and mental arithmetic stress.

Methods: Twenty patients with CRPS and 20 age-, sex-, and body mass index-matched control subjects participated. Mean values of heart rate variability, baroreceptor sensitivity, blood pressure, stroke volume, cardiac output, and total peripheral resistance were estimated during supine rest and 60° tilt-table testing. On a separate day, heart rate variability was also measured during mental arithmetic stress testing induced by a paced auditory serial addition task.

Results: Heart rate was increased and heart rate variability reduced in patients with CRPS compared with control subjects during rest and mental and orthostatic stress,

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Received from the Danish Pain Research Center and Department of Neurology, Aarhus University Hospital, Aarhus, Denmark. Submitted for publication December 21, 2010. Accepted for publication July 22, 2011. Supported by grants from the Danish Council for Independent Research: Medical Sciences, Copenhagen, Denmark (271-07-0396); King Christian IX and Queen Louises Jubilee Fund, Klampenborg, Denmark (26-09-06); the Research Initiative of Aarhus University Hospital, Aarhus, Denmark (2-16-4-14-05); the Pain Research Foundation, Copenhagen, Denmark (22-08-06); Alice and Jørgen A. Rasmussens Memorial Award, Nærum, Denmark (04-09-07); the Senior Resident Foundation, Aalborg Hospital, University Hospital of Aarhus, Aalborg, Denmark (18-02-08); and Sanatorielæge Ellen Pedersens Foundation, Ry, Denmark (01-07-08). The authors have no conflicts of interest.

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What We Already Know about This Topic

- Autonomic and vascular changes are associated with both acute and chronic complex regional pain syndrome, but the underlying mechanisms are unknown

What This Article Tells Us That Is New

- Heart rate was increased and heart rate variability reduced in patients with complex regional pain syndrome consistent with a general autonomic imbalance in cardiovascular regulation
- This was also evident in an exaggerated reduction in cardiac output in response to orthostatic stress

whereas baroreceptor sensitivity was unaffected. When tilted from supine to upright position, patients with CRPS were not able to preserve cardiac output in comparison with control subjects, and they exhibited an exaggerated increase in the total peripheral resistance. The hemodynamic changes correlated to pain duration but not to pain intensity.

Conclusion: The increased heart rate and decreased heart rate variability in CRPS suggest a general autonomic imbalance, which is an independent predictor for increased mortality and sudden death. The inability of the patients to protect their cardiac output during orthostatic stress was aggravated with the chronicity of the disease.

COMPLEX regional pain syndrome (CRPS) type I (without nerve lesion) and type II (with nerve lesion) is a chronic pain condition characterized by spontaneous and evoked pain, usually in distal parts of extremities and with both sensory and autonomic changes. The pathophysiology is not known in detail, and factors such as limb immobilization,¹ ischemia with reperfusion,² small-fiber neuropathy,³ neurogenic inflammation,⁴ sympathetic denervation followed by supersensitivity,⁵ and genetic mechanisms⁶ have all been suggested to play a pathophysiologic role. CRPS is often divided into two subtypes: an acute warm and vasodilated state and a chronic cold state with vasoconstriction. The acute warm state has been linked to partial sympathetic denervation⁵ and neurogenic inflammation,⁴ whereas denervation supersensitivity with secondary up-regulation of α -adrenoceptors is suggested to be responsible for the more chronic cold state.⁷ These findings suggest that vascular changes are associated with both acute and chronic CRPS.

Previously, the focus has mainly been on local autonomic and vascular changes, but other findings point to systemic autonomic and vascular abnormalities in CRPS. First, patients with CRPS have increased concentrations of catecholamines in venous plasma in comparison with healthy control subjects.⁸ Second, the sympathetic vasoconstrictor reactivity in acute CRPS is reported to be diminished in the affected and contralateral hands and also in upper limbs in patients with leg involvement.⁹ Third, increased numbers of skin α 1-adrenoceptors¹⁰ and dorsal superficial vein hyperresponsiveness to noradrenaline⁷ are reported in limbs affected and unaffected by CRPS. Fourth, the regional osteoporosis, in part regulated by the sympathetic nervous system, and pain may spread to involve the other limb, and occasionally affect all four extremities.^{11,12} These findings suggest that CRPS might be a disorder with general autonomic and vascular changes.

The general balance of autonomic activation can be studied by measuring the increase in heart rate, the decrease in heart rate variability, and the baroreceptor sensitivity in response to stress.^{13,14} The baroreceptor reflex is involved in short-term blood pressure regulation. Heart rate variability is a quantitative measure of the balance between the parasympathetic and sympathetic regulation of cardiac activity, and based on power spectral analysis it is possible to separate cardiac parasympathetic activity from sympathetic activity.¹⁵

Apart from changes in heart rate and heart rate variability, a general autonomic activation induces systemic cardiovascular changes with increased blood pressure, cardiac output, skeletal muscle blood flow, and release of stress hormones^{16,17}; the systemic cardiovascular involvement can be evaluated by measuring blood pressure, stroke volume, cardiac output, and total peripheral resistance.

The primary aim of this study was to determine whether heart rate variability and baroreceptor sensitivity are reduced in patients with CRPS during rest and during activation of the autonomic nervous system by orthostatic and mental arithmetic stress as a marker of a general autonomic dysregulation. The secondary aim was to test the systemic cardiovascular responses to orthostatic stress.

Materials and Methods

Participants received a written and oral explanation of the study and signed an informed consent document. The study was carried out according to the Declaration of Helsinki and approved by the Local Ethical Committee (No. 20050192), Viborg, Denmark and the Danish Data Protection Agency. The experiment was registered at clinicaltrials.gov (NCT00560131).

Patients with CRPS

Patients with CRPS attending the Neuropathic Pain Clinic at Aarhus University Hospital, Aarhus, Denmark were recruited together with other patients with CRPS in Jutland. Patients were required to fulfill the recently approved re-

search diagnostic criteria for CRPS.¹⁸ Briefly, these are continuing pain disproportionate to any inciting event, together with at least one symptom in each of the four following categories, and at least one sign in two or more of the four following categories: sensory, vasomotor, sudomotor/edema, or motor/trophic disturbances. For technical reasons it was impossible to measure oscillometric blood pressure in one patient. This patient was excluded before tilting, leaving data from 20 patients with CRPS.

Healthy Control Subjects

Healthy control subjects matched the patients with CRPS with respect to age, sex, and four body mass index (BMI) intervals (less than 18.5, 18.5–24.9, 25–29.9, > 30 kg/m²), parameters affecting autonomic and hemodynamic measures. Control subjects were recruited by advertising at Aarhus University Hospital. Inclusion criteria were a normal physical examination and a medical history without a past history of fainting. Twenty control subjects were included in the tilt-table and mental stress testing. In the mental stress control group, two subjects refused to participate after participation in the tilt session and were substituted with two others. In the tilt control group, five subjects had syncope or had marked near-syncope symptoms and were substituted by six others (one of these was subsequently excluded). In the two control groups consisting of 20 age-, sex-, and BMI-matched control subjects, 13 participated in both tests.

Exclusion Criteria

Syncope during tilt-table testing, age younger 18 yr, previous sympathectomy, an abnormal electrocardiogram, significant cardiovascular disease, pharmacologic treatment potentially affecting the cardiovascular or autonomic system, malignancy, infection with human immunodeficiency virus, diabetes, hypertension, pregnancy, lactation, alcoholism, or drugs of abuse.

Experimental Setup

To minimize external autonomic influences, tests were performed in a quiet room with dim lighting and at a constant mean room temperature of 23.5°C (SD 0.9°C). Patients and control subjects fasted for at least 2 h before testing, emptied their bladder, and were not allowed to talk during testing. All participants refrained from smoking, alcohol consumption, and caffeine-containing beverages for at least 12 h and from excessive physical activity for at least 24 h before the experimental sessions, and did not participate in medical experiments the previous 2 months.

Course of Examination

Subjects participated on three separate days. Day 1: Inclusion. A medical history and clinical examination were obtained. Day 2: Tilt-table testing was performed between 10 AM and 12 PM by the same experimenter (AJT) and an experienced medical laboratory technician. Subjects rested in a

supine position for 30 min before recording. Heart rate, heart rate variability, baroreceptor sensitivity, respiratory rate, and cardiovascular parameters were continuously measured during 10 min supine rest (baseline), two times 10 min in upright tilted position, and during 10 min supine recovery. Day 3: Mental arithmetic stress sessions were performed by AJT. Subjects rested in a supine position for 30 min before recording. Heart rate and heart rate variability were continuously measured and estimated during 5 min of rest and 5 min of mental arithmetic stress induced by a paced auditory serial addition task (PASAT).

Medical History

A medical history was obtained and patients completed the Danish version of the McGill Pain Questionnaire.¹⁹ Using a numeric pain rating scale 0–10 (0 = no pain, 10 = maximal imaginable pain) the patients rated spontaneous pain intensity, mean pain the past 24 h, and the highest pain intensity the past 24 h. Furthermore, they marked the areas of spontaneous pain on a body chart (anterior and posterior dimensions) and described whether the affected extremity was intermittently warmer, colder, or constantly had the same temperature as the unaffected extremity.

Clinical Examination

A physical and neurologic examination was done. Areas of pinprick hyperalgesia and brush allodynia were mapped on a body chart (anterior and posterior dimensions). Pinprick hyperalgesia was induced by a single punctate (pinprick) stimulus (von Frey monofilament, estimated force 745 mN; Semmes-Weinstein monofilament, Stoelting, IL). Brush allodynia or dysesthesia was provoked by brushing at 5 cm/s (SENSELab, Brush-05, Somedic Sales AB, Hörby, Sweden).

Mental Arithmetic Stress Induced by PASAT

PASAT^{20,21} consisted of an auditory presentation of random digits from 1 to 9 with an interval of 2.4 s between digits. The subject's task was to continuously express the sum of the two last digits. The percentage of correct answers for 5-min periods was calculated.

Orthostatic Stress (Tilt-Table Test)

Tilt-table testing was performed according to the Westminster protocol²² by tilting subjects from supine to erect posture (60°). To obtain stationary signals after changing position, measurements were started 4 min after tilting to the upright position and 3 min after returning to the supine position. The tilt-table (Follo A/S, AaS, Norway) had a footboard support and achieved the upright (20 s) and supine position (18 s) smoothly and rapidly.

Autonomic and Hemodynamic Parameters during Tilt-Table Testing

The Task Force Monitor (CNSystems Medizintechnik AG, Graz, Austria) noninvasively recorded electrocardiogram, os-

cillometric and beat-to-beat blood pressure, impedance cardiography, and respiration.²³ Autonomic and hemodynamic parameters were estimated and expressed as mean values of baroreceptor sensitivity, systolic and diastolic blood pressure, stroke volume, cardiac output, total peripheral resistance, and respiration. Using an upper arm cuff on the affected extremity in patients and on the matched arm in control subjects, oscillometric blood pressure recordings were initially performed three times and thereafter every 5 min or after any change in position. Beat-to-beat blood pressure was recorded at the second or third finger on the contralateral hand by the vascular unloading of the finger arterial walls using an inflatable finger cuff with a built-in photoplethysmographic sensor²⁴ and with automatic correction to the oscillometric blood pressure. Impedance band electrodes were placed in the area between the patient's neck and the hairline and the other two as parallel as possible at the lateral side of the thorax at the xiphoid level. The impedance cardiography signal was used for the estimation of stroke volume²⁵ by detecting the aortic opening and closing points.²⁶ The clinical gold standard for measuring stroke volume is thermodilution. However, this invasive method activates the autonomic nervous system. In contrast, impedance cardiography is noninvasive, safe, easy to use, and capable of long-term and continuous beat-to-beat recordings, making it possible to detect trends and acute hemodynamic changes induced by tilt-table testing. This technique has low within-technique variability, a high reproducibility in hemodynamically stable patients,^{23,25,27} and is recommended for the evaluation of relative changes.²⁵

Cardiac output was estimated as stroke volume times the heart rate. The total peripheral resistance was estimated as ((mean arterial blood pressure – central venous pressure)/cardiac output) × 80 where the default setting of the central venous pressure is 3 mmHg. The respiratory rate was quantified by the impedance electrode positioned around the ribs. The spontaneous baroreflex activity was analyzed offline by the Task Force Monitor by means of the Sequence-Method,²⁸ which analyzes and displays rising/falling sequences (progressive increase/decrease in systolic blood pressure and lengthening/shortening in the RR intervals (the distance in ms between consecutive normal R waves in the QRS complexes) separately over more than three consecutive beats. The QRS complex is the name for some of the deflections seen on a typical electrocardiogram. The minimum change accepted as a spontaneous increase or decrease in systolic blood pressure and RR interval was 1 mmHg and 4 ms, respectively. The mean slope of all regression lines between RR intervals and systolic blood pressure sequences represented the baroreceptor sensitivity. In the current material, the baroreceptor sensitivity could not be estimated in two healthy control subjects during supine and recovery periods due to absent events.

QRS Detection and Heart Rate Variability Expressed in the Time and Frequency Domain

Raw data from electrocardiogram, lead II (sample rate: 1,000 Hz) were exported to custom-made software to detect QRS complexes, verify their correctness, and correct for noise or arrhythmic behavior.¹⁵ This is not an option in the Task Force Monitor software. QRS detection was done with an algorithm similar to that presented by Pan and Tompkins.²⁹ False detections were deleted and periods with missing beats were corrected by interpolation. Nine and six ectopic QRS complexes were replaced in the CRPS and control groups, respectively. Time domain measures included the RR interval, the SD of all normal RR intervals, and the square root of the mean squared differences of successive RR intervals (RMSSD). RMSSD is not influenced by mean resting heart rate and estimates high-frequency variation in heart rate.¹⁵ Power spectral analysis requires equidistantly sampled data. Accordingly, the nonequidistant RR interval time series were interpolated with a cubic spline method and resampled at a higher, uniform rate of 4 Hz. Each time section had the static component removed (making it zero mean). Autoregressive power spectrum estimations with a model order of 20 were performed.³⁰ High-frequency (HF) power (0.15–0.4 Hz) is considered an index of cardiac vagal activity, whereas low-frequency (LF) power (0.04–0.15 Hz) is a baroreflex-mediated response affected by both sympathetic and parasympathetic activity.¹⁵ Each power spectral component was expressed in absolute units, normalized units (power/(total power - very-low (< 0.03 Hz) frequency oscillations)), the coefficient of component variance in the LF and HF bands (square root of LF or HF power/RR interval).³¹ The coefficient of component variance in the LF and HF bands adjusts for influences of different RR intervals on the power amplitude because saturation of the sinus node by a very high sympathetic or parasympathetic drive is proposed to make the sinus node less capable of maintaining a rhythmic modulation.^{32,33} The LF:HF ratio was calculated as the normalized LF power divided with the normalized HF power.¹⁵

Statistical Analysis

Measurements were summarized by computing arithmetic mean and SD. To accommodate the assumptions of normal distributions, the SD of all normal RR intervals and the frequency domain parameters were log-transformed before analysis and summarized by geometric means and coefficients of variation. Differences and CIs for log-transformed data were back-transformed and expressed as the ratio (patient/control subject) of medians with CIs. Fisher exact test was used to compare the proportion of smokers in the patient and control group. Unpaired Student *t* tests were used to test differences in age, weight, height, and BMI between the patient and control groups. Hemodynamic and autonomic parameters were compared by using two-way repeated measures analysis of covariance (ANCOVA) with smoking (yes, no) as a covariate. The condition \times group interaction and

the main effect of the condition and the group were assessed. If the condition \times group interaction was statistically significant (nonparallel profiles) this analysis was, for the secondary effect parameters, supplemented by a comparison of the absolute differences and of the relative changes between groups. To adjust for smoking these comparisons were performed by a multiple regression analysis. For parallel profiles mean ratio/difference for the four time points and CI was reported. Correlations were tested with Spearman rank test. All statistical tests were two-sided, and the level of significance was 5%. Stata 8.1 (StataCorp. 2003, Stata Statistical Software: Release 8.0. College Station, TX: Stata Corporation) was used for the basic statistical calculations.

Results

Participant Characteristics

Twenty patients with CRPS (12 F, 8 M), mean age 43 yr (SD 12) and mean BMI 26 kg/m² (SD 5) were included. Twenty healthy control subjects (12 F, 8 M), mean age 43 yr (SD 14) and mean BMI 26 kg/m² (SD 4), participated in the tilt-table test and 20 control subjects (12 F, 8 M), mean age 41 yr (SD 13) and mean BMI 26 kg/m² (SD 5), participated in the PASAT test. Sex, age, weight, height, and BMI were comparable in patients and control subjects. More patients (45%) than control subjects (10%) were active smokers ($P = 0.03$). Seventy percent of the patients were immobilized before the development of CRPS. Sixteen had upper, three had lower, and one had both upper and lower limb affection (table 1).

Medication in individual healthy control subjects: citalopram 10 mg/day, not taken the previous 10 days; dicloxacillin 750 mg/day (for recovered cutaneous staphylococcus infection), not taken the previous 2 days; lansoprazole 15 mg/day, not taken the previous 2 days; levothyroxine 100 μ g/day, not taken the previous 1 day; tetracycline 500 mg/day (for recovered acne vulgaris), not taken the previous 2 days; fluticasone nasal spray 50 μ g/dose; gestodene 75 μ g and ethinylestradiol 30 μ g (contraceptives); drospirenone 3 mg and ethinylestradiol 30 μ g (contraceptives); nonsedating antihistamines in two subjects, not taken the previous 2 days.

Pain Characteristics in CRPS

As shown in figure 1, spontaneous pain, allodynia, and hyperalgesia were distally localized and not limited to the territory of a single peripheral nerve. Pain ratings in patients with CRPS assessed by a numeric pain rating scale and expressed as mean \pm SD (range) were spontaneous pain intensity: 4.9 \pm 2.8 (0–10); mean pain the past 24 h: 6.2 \pm 2.4 (1–9); the highest pain intensity the past 24 h: 7.9 \pm 1.8 (4–10). Pain duration was 1,252 \pm 1,496 (26–6,234) days including one acute (≤ 3 months with pain) and 19 patients with chronic CRPS (table 1).

Patients commonly complained of pins and needles/tin-gling, burning, pressing/squeezing, paroxysmal, and evoked pain. The most common sensory descriptors of pain were

Table 1. Demographic Data and Medication for CRPS Patients

Patient No.	Age/ Sex	Imm. (d)	Reported Skin Temp.	Inciting Event, Affected Extremity	Pain Duration	Medication	NRS-24 h
1	46/M	3	Warm	Ulnar nerve compression, nerve conduction study, L	26 d	PCT 3 g/d and ibuprofen 1,800 mg/d; not taken the previous 1 d	6
2	36/M	33	Warm	Tibial and fibular fracture, L	154 d	—	3
3	48/M	35	Warm	Distal radius fracture, L	173 d	Escitalopram 20 mg/d and oxazepam 15 mg/d; not taken the previous 2 d. GBP 1,200 mg/d, not taken the previous 10 d	8
4	38/F	24	Warm/cold	Distortion of wrist, R	182 d	PCT 3 g/d and ibuprofen 1,200 mg/d; not taken the previous 12 h	9
5	30/F	44	Cold	Strain of digit 1, L	346 d	PCT 4 g/d, GBP 2,400 mg/d, desloratadine 5 mg/d, oxycodon immediate-release 20 mg/d, and ondansetron 12 mg/d; not taken the previous 12 h	6
6	44/F	0	Warm/cold	No trauma, L arm	455 d	GBP 1,800 mg/d, not taken the previous 5 d	6
7	19/F	77	Warm/cold	Surgical revision of ulcer, R hand	565 d	—	8
8	59/M	126	ND	Clavicle fracture, R	785 d	PCT 4 g/d and mirtazapine 15 mg/d; not taken the previous 10 d. GBP 1,600 mg/d, not taken the previous 4 d	8
9	38/M	28	Cold	Surgical decompression of ulnar nerve, L	790 d	PCT 2 g/d and tramadol 300 mg/d; not taken the previous 3 d. Amitriptyline 25 mg/d, not taken the previous 9 d. GBP 2,400 mg/d, not taken previous 2 d	7
10	33/M	0	Warm/cold	Ulnar nerve lesion, R	889 d	PCT 3 g/d and tramadol 300 mg/d; not taken the previous 2 d	9
11	30/F	60	Cold	Ankle strain, R	961 d	PGB 600 mg/d and topiramate 75 mg/d; not taken the previous 12 h	7
12	50/F	0	Cold	Surgical release of Dupuytren's contracture, L	1,077 d	—	5
13	34/F	29	Cold	Crush injury with comminuted fracture of digit 2, L	1,080 d	Oxycodon immediate-release 60 mg/d and oxycodon sustained-release 20 mg/d	8
14*	38/F	0	Warm/cold	Trauma against elbow. Spinal cord contusion, R	1,127 d	PCT 2 g/d and ibuprofen 200 mg; not taken the previous 12 h	8
15	56/F	47	Cold	Distal radius fracture, R	1,231 d	—	2
16	39/M	86	ND	Open luxation of distal interphalangeal joint of digit 1, R	1,357 d	—	7
17	62/F	28	Warm/cold	Distal radius fracture, L	1,407 d	Levothyroxin 75 μ g/d, not taken the previous 1 d	1

(continued)

Table 1. Continued

Patient No.	Age/ Sex	Imm. (d)	Reported Skin Temp.	Inciting Event, Affected Extremity	Pain Duration	Medication	NRS-24 h
18	40/F	0	Warm/cold	Traumatic rupture of the cruciate knee ligament, L	1,838 d	PCT 4 g/d, tramadol 200 mg/d, and diclofenac 300 mg/d, not taken the previous 3 d	7
19	57/F	0	Warm/cold	Knee arthroscopy, L	4,362 d	Codeine 100 mg/d, not taken the previous 2 d. PCT 4 g/d	7
20	64/M	3	Cold	Infection in hand after dog bite, R	6,234 d	Telfast 120 mg/d, not taken previous 3 d	2

* 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.

Cold = colder affected extremity; CRPS = complex regional pain syndrome; F = female; GBP = gabapentin; Imm. = immobilization; L = left; M = male; ND = no temperature difference; NRS-24 h = the mean pain the last 24 h rated on a numeric pain rating scale; PCT = paracetamol (acetaminophen); PGB = pregabalin; R = right; Reported skin temp. = reported skin temperature of the affected extremity compared with the unaffected extremity; Warm = warmer affected extremity.

“throbbing,” “shooting,” “pricking and boring,” “hot and scalding,” “tingling,” and “taut” according to the McGill Pain Questionnaire.¹⁹ The McGill Pain Questionnaire scores (mean \pm SD) were as follow: pain rating index, 46.5 (12.4); total number of words chosen, 17.9 (2.9); pain rating index-sensory, 20.7 (5.4); pain rating index-affective, 12.8 (4.6).

PASAT Performance

The mean PASAT performance of 56% (SD 19) in patients was lower than the mean performance 75% (SD 15) in control subjects ($P = 0.002$), and 85% ($n = 17$) of the patients performed less well than the matched control.

Heart Rate Variability and Baroreceptor Sensitivity during Baseline Conditions and during Mental and Orthostatic Stress

As shown in tables 2–4 at baseline and during mental and orthostatic stress, heart rate was higher (reduced RR intervals) and heart rate variability lower (reduced SD of all normal RR intervals) in patients with CRPS in comparison with control subjects, whereas baroreceptor sensitivity failed to reach statistical significance.

During rest and orthostatic stress, RMSSD, LF power, HF power, LF:HF ratio, and total power did not differ between groups (table 2).

During rest and mental stress, absolute LF power, total power, and indexes of parasympathetic activity (RMSSD and absolute HF power) were decreased in patients compared with control subjects (table 3). Mentally stressed control subjects and patients with resting CRPS had (apart from the parasympathetic measures) similar autonomic values (table 3).

Despite the reduced PASAT performance in the patients, the relative PASAT-induced changes of the autonomic measures were similar in the two groups (statistics not reported in the tables).

Hemodynamic Parameters during Supine Rest, Orthostatic Stress, and Supine Recovery

Figure 2A shows an example of the hemodynamic response to orthostatic stress in a healthy control subject. The abnormal hemodynamic response in CRPS is illustrated in figure 2B.

Patients had a significant reduction in cardiac output when tilted from supine to upright position during the first ($P = 0.03$; 16% *vs.* 2% reduction, fig. 3) and second ($P = 0.02$; 14% *vs.* -1% reduction, fig. 3) periods in upright position that persisted during recovery ($P = 0.01$; 6% *vs.* 0%). During the same orthostatic manipulations there was a corresponding significant increase in total peripheral resistance (fig. 3).

The continuously measured systolic blood pressure and stroke volume did not show any significant differences (table 4). The respiratory rate was increased in patients in comparison with control subjects (table 2).

Smoking Adjustment

For the respiratory rate ($P = 0.11$) measured during tilt-table test and for RMSSD ($P = 0.08$) and absolute HF power ($P = 0.11$) measured during mental stress, the P values became significant after smoking adjustment. This was not the case for other parameters.

Pain and Hemodynamic Parameters

To further assess the role of pain *per se* for the current systemic changes, we determined the possible relationship between orthostatic-induced changes in cardiac output and vascular resistance and pain duration and intensity. The reduction in cardiac output during the upright position was inversely correlated with pain duration ($r = -0.6$, $P = 0.005$; fig. 4) but not pain intensity ($r = -0.04$, $P = 0.9$, fig. 4). During the upright position, the increase in total peripheral resistance was significantly correlated with pain duration ($r = 0.7$, $P = 0.002$; fig. 4) but not pain intensity ($r = 0.03$, $P = 0.9$; fig. 4).

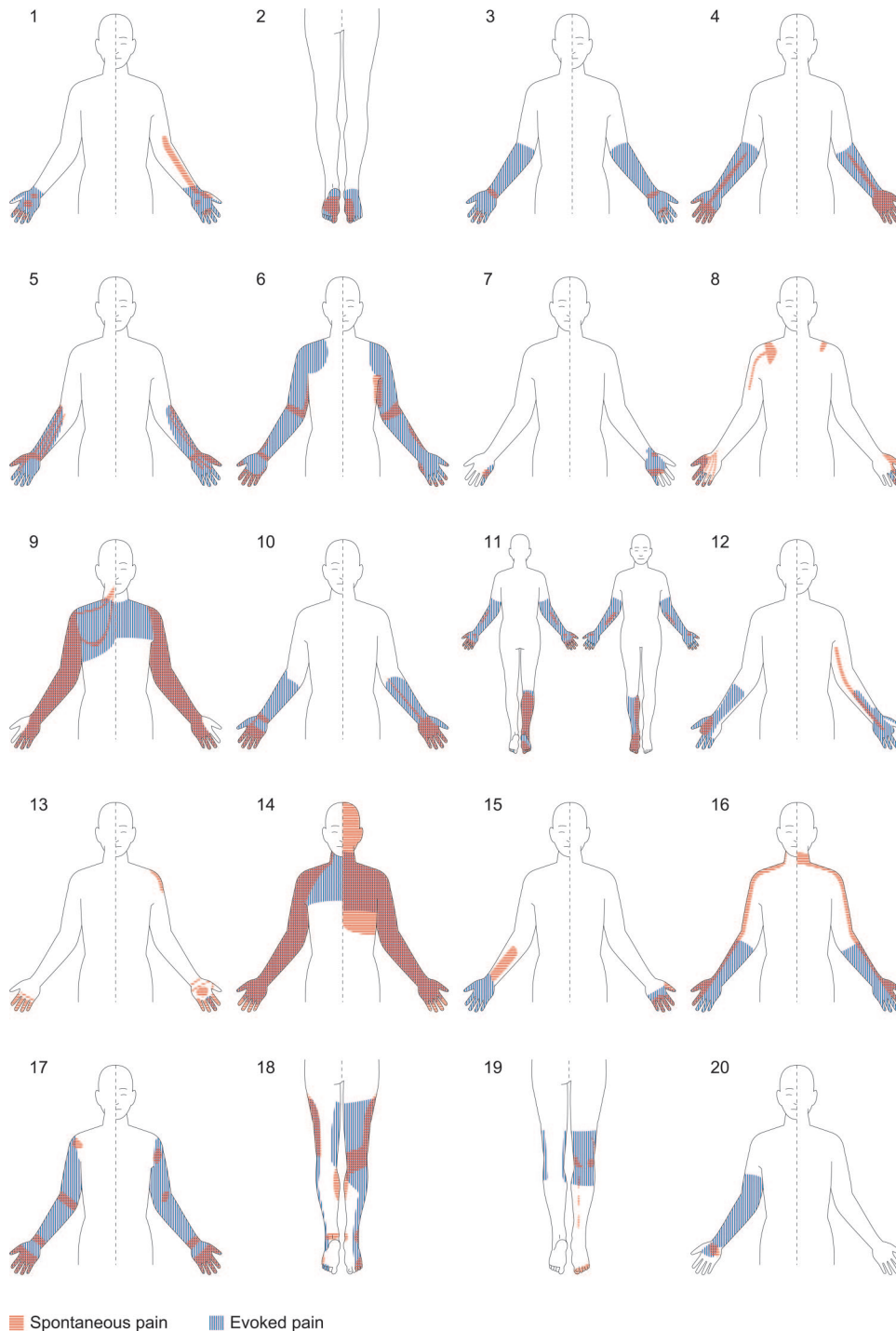


Fig. 1. Areas of spontaneous and evoked pain (pinprick hyperalgesia and brush allodynia) marked on a body chart (posterior and anterior dimensions) in patients with complex regional pain syndrome.

Discussion

Heart Rate and Heart Rate Variability

The primary finding was increased heart rate and reduced heart rate variability during rest and during mental and orthostatic stress in patients with CRPS compared with control subjects. Patients with resting CRPS and mentally stressed healthy subjects had, apart from the parasympathetic activation,

an identical autonomic profile, indicating a clear autonomic activation in the patients.

The current reduced heart rate variability indicates that the overall sympathetic and parasympathetic influence on the heart is changed.¹⁵ However, the normalized measures showed no changes in the relative magnitude of the HF and LF components beyond an overall decrease in the total power in the signal in the patients. Therefore, probably due

Table 2. Heart Rate Variability and Respiratory Rate Measured during Rest, Tilt-Table Testing, and Recovery in Patients and Controls

	Baseline	Upright 1	Upright 2	Recovery	ANCOVA (<i>P</i> Value)	
					Condition × Group	Between-Group
RR interval [ms]*						
Control subjects	1,074 (165)	860 (135)	832 (133)	1,104 (171)	<.001	.004
Patients	927 (121)	782 (111)	752 (111)	933 (127)		
SDNN [ms]†						
Control subjects	54 (45)	45 (47)	44 (44)	62 (57)	.99	.02
Patients	44 (40)	37 (22)	35 (32)	50 (38)		
RMSSD [ms]*						
Control subjects	53 (41)	23 (11)	21 (11)	66 (65)	.22	.07
Patients	37 (20)	18 (8)	17 (9)	42 (26)		
LF power [ms ² /Hz]†						
Control subjects	599 (88)	476 (92)	493 (128)	890 (88)	.99	.21
Patients	425 (76)	346 (73)	354 (111)	623 (89)		
LF power [n.u.]*						
Control subjects	47 (16)	69 (13)	73 (11)	53 (19)	.59	.33
Patients	50 (17)	68 (12)	70 (12)	55 (14)		
HF power [ms ² /Hz]†						
Control subjects	606 (182)	143 (71)	112 (86)	690 (231)	.53	.09
Patients	357 (130)	101 (124)	95 (142)	414 (109)		
HF power [n.u.]*						
Control subjects	47 (16)	24 (12)	19 (9)	42 (19)	.31	.22
Patients	43 (18)	23 (12)	22 (12)	38 (15)		
LF:HF ratio*						
Control subjects	1.2 (0.8)	4.5 (3.7)	5.7 (4.6)	1.8 (1.3)	.59	.43
Patients	1.6 (1.3)	4.6 (4.0)	4.9 (3.6)	1.9 (1.4)		
Total power [ms ² /Hz]†						
Control subjects	1,357 (127)	702 (82)	682 (115)	1,833 (169)	.90	.13
Patients	908 (98)	513 (84)	512 (119)	1,176 (93)		
Respiration [breath/min]*						
Control subjects	16.6 (2.2)	16.9 (1.4)	16.9 (1.5)	17.0 (1.9)	.76	.04
Patients	17.5 (1.7)	17.7 (1.8)	17.8 (1.9)	17.5 (1.5)		

Hemodynamic parameters measured during: 10 min supine rest (Baseline), two times 10 min in 60° upright position (Upright 1, Upright 2), and during 10 min supine recovery (Recovery).

* Values presented as mean (SD) and mean differences and CI expressed as absolute values. † Values presented as mean (coefficient of variation [%]) and mean ratio [%] and CI estimated by backtransforming log-transformed data and expressed as the ratio of medians in percent. Autonomic responses were compared by using repeated measures analysis of covariance (ANCOVA). The condition × group interaction and the main effect of the group (between-group) is reported. ‡ For parallel profiles, mean diff./ratio [CI] for the four time points is reported.

HF and LF power = high and low frequency power expressed in absolute values [ms²/Hz] and [n.u.]; LF:HF ratio = normalized LF power divided with normalized HF power; ms = milliseconds; n.u. = normalized units; RMSSD = the square root of the mean squared differences of successive RR intervals; RR interval = mean time between consecutive normal R waves in the QRS complexes; SDNN = SD of all normal RR intervals.

to a small sample size, we could not determine whether the changes were due to reduced parasympathetic activity, increased sympathetic activity, or a combination of both events.

Subjects performed the mental arithmetic stress test aloud and had an increased respiratory rate during tilt, raising the possibility that respiration influenced the autonomic outcomes.³⁴ However, this small change in the respiratory interval cannot explain the difference in heart rate variability and would never affect the RR interval.

Increased heart rate and reduced heart rate variability both have been linked to anxiety,³⁵ depression,³⁶ and physical inactivity.³⁷ These covariates were not controlled for in this study but should be assessed in future studies. Whatever

the reason, reduced heart rate variability is an independent predictor for increased mortality and sudden death.³⁸

Systemic Cardiovascular Dysfunction during Tilt-Table Testing

Patients with CRPS had hemodynamic dysfunction with a considerable reduction in cardiac output when tilted to an upright position that persisted after returning to a supine position. Furthermore, they exhibited an exaggerated increase in the total peripheral resistance to the upright position. The pain duration was inversely correlated with the tilt-induced reduction in cardiac output and correspondingly, as peripheral resistance is calculated from this measure, correlated to the increase in vascular resistance (fig. 4) with

Table 3. Heart Rate Variability Measured during Rest and Mental Arithmetic Stress Testing in Patients and Control Subjects

	Baseline	Mental Stress	ANCOVA (<i>P</i> Value)	
			Condition × Group	Between-Group
RR interval [ms]				
Control subjects	1,061 (175)	904 (178)	.15	.003
Patients	908 (117)	796 (128)	−154 [−254 to −55]*	
SDNN [ms]				
Control subjects	58 (58)	47 (36)	.99	.01
Patients	44 (42)	35 (48)	72 [56–93]†	
RMSSD [ms]				
Control subjects	55 (51)	31 (20)	.39	.047
Patients	36 (20)	21 (16)	−18 [−35 to −0.2]*	
LF power [ms ² /Hz]				
Control subjects	793 (105)	445 (93)	.63	.02
Patients	398 (66)	262 (98)	51 [29–89]§	
LF power [n.u.]				
Control subjects	54 (19)	62 (14)	.16	.52
Patients	50 (18)	65 (11)	3 [−6 to 12]*	
CCV-LF [%]				
Control subjects	2.7 (54)	2.4 (34)	.34	.11
Patients	2.2 (37)	2.1 (43)	31 [7–134]†	
HF power [ms ² /Hz]				
Control subjects	580 (242)	182 (116)	.72	.04
Patients	339 (168)	94 (159)	43 [19–95]†	
HF power [n.u.]				
Control subjects	41 (20)	28 (13)	.30	.39
Patients	43 (19)	25 (10)	−4 [−13 to 5]*	
CCV-HF [%]				
Control subjects	2.3 (91)	1.5 (56)	.81	.29
Patients	2.0 (72)	1.2 (60)	29 [3–301]†	
LF:HF ratio				
Control subjects	2.0 (1.8)	3.5 (3.5)	.76	.79
Patients	1.7 (1.4)	3.4 (2.4)	0.2 [−1.2 to 1.6]*	
Total power [ms ² /Hz]				
Control subjects	1,596 (163)	735 (93)	.94	.02
Patients	871 (114)	410 (121)	48 [26–88]†	

Autonomic parameters were compared by using repeated-measures analysis of covariance (ANCOVA). The condition × group interaction and the main effect of the group (between-group) is reported. Values are presented as mean (SD/coefficient of variation [%]).

* Mean difference and confidence intervals [CI] are expressed as absolute values. † Mean ratio and CI are estimated by backtransforming log-transformed data and expressed as the ratio of medians in percent. The gray box illustrates identical measures in resting patients and stressed control subjects.

CCV-HF, CCV-LF = coefficient of component variance in the HF and LF band; HF and LF power = high- and low-frequency power expressed in absolute values [ms²/Hz] and [n.u.]; LF:HF ratio = normalized LF power divided with normalized HF power; ms = milliseconds; n.u. = normalized units; RMSSD = the square root of the mean squared differences of successive RR intervals; RR interval = mean time between consecutive normal R waves in the QRS complexes; SDNN = SD of all normal RR intervals.

most pronounced hemodynamic changes in patients having the longest duration of the disorder.

Under normal physiologic circumstances, the migration of blood from the thorax to the lower parts of the body while in the upright position reduces the venous return and consequently the stroke volume³⁹ and is followed by decreased vagal tone and increased sympathetic tone.⁴⁰ The response is stabilized after some minutes with a slight increase in heart rate and vascular resistance. Usually, as in our participants, systolic and diastolic blood pressures are slightly increased or unchanged. The response is associated with a decreased cardiac output, but in most cases, as in our study, the heart rate increase fully compensates for the decrease in venous return.

In the control subjects we found a normal hemodynamic response to tilt (figs. 2 and 3). However, in the patients with CRPS (figs. 2 and 3) the cardiac output was significantly decreased while in the upright position and not followed by a compensatory increase in heart rate. To avoid compensatory reductions in the arterial pressure, the vascular resistance was increased significantly more in patients during upright positioning. Changes in muscle sympathetic nerve activity during postural change are inversely related to the resting level of nerve activity,⁴¹ in accordance with the current tendency of a lower resting total peripheral resistance, but an exaggerated increase in total peripheral resistance in the patients during orthostatic stress.

Table 4. Hemodynamic Responses and Baroreceptor Sensitivity Measured during Rest, Tilt-Table Testing, and Recovery in Patients and Control Subjects

	Baseline	Upright 1	Upright 2	Recovery	ANCOVA (P Value)	
					Condition × Group	Between- Group
ContSBP [mmHg]						
Control subjects	124 (16)	130 (17)	129 (17)	126 (17)	.46	.48
Patients	124 (17)	131 (18)	133 (17)	128 (14)	4 [−7 to 15]*	
ContDBP [mmHg]						
Control subjects	81 (11)	91 (12)	90 (12)	81 (11)	.03	.47
Patients	81 (12)	89 (13)	91 (13)	84 (10)		
<i>P</i>	.72	.88	.35	.15		
Diff. (CI)	1 [−7 to 10]	1 [−8 to 9]	4 [−4 to 12]	5 [−2 to 13]		
Baroreceptor sensitivity [ms/ mmHg]						
Control subjects	22 (14)	10 (5)	9 (5)	23 (16)	.18	.12
Patients	17 (9)	8 (3)	8 (3)	17 (9)	−4 [−9 to 1]*	
Stroke volume [ml]						
Control subjects	99 (22)	77 (17)	76 (17)	101 (22)	.14	.07
Patients	98 (23)	67 (15)	66 (15)	92 (23)	−11 [−23 to 1]*	
Cardiac output [l/min]						
Control subjects	5.5 (1.0)	5.4 (1.0)	5.6 (1.1)	5.5 (1.0)	<.001	.85
Patients	6.3 (1.4)	5.2 (1.0)	5.3 (1.0)	5.9 (1.3)		
<i>P</i>	.12	.47	.37	.63		
Diff. (CI)	.7 [−.2 to 1.5]	−.3 [−1.0 to .5]	−.3 [−1.1 to .4]	.2 [−.6 to 1.0]		
Total peripheral resistance [dynes · s · cm ^{−5}]						
Control subjects	1,371 (379)	1,545 (465)	1,495 (414)	1,369 (332)	.01	.66
Patients	1,182 (322)	1,582 (520)	1,589 (488)	1,347 (354)		
<i>P</i>	.28	.47	.24	.67		
Diff. (CI)	−134 [−378 to 111]	124 [−216 to 464]	184 [−126 to 494]	50 [−185 to 284]		

Hemodynamic parameters measured during: 10 min supine rest (Baseline), two times 10 min in 60° upright position (Upright 1, Upright 2), and during 10 min supine recovery (Recovery). Values presented as mean (SD). Hemodynamic parameters were compared by using repeated-measures analysis of covariance (ANCOVA). The condition × group interaction and the main effect of the group (between-group) is reported. At significant condition × group interaction statistical comparison of the absolute differences for each condition is reported with mean difference (diff.) and CI. The significant relative changes in cardiac output and total peripheral resistance are reported in the results section.

*For parallel profiles mean diff. [CI] for the four time points is reported.

ANCOVA = analysis of covariance; ContDBP = mean of continuously measured diastolic blood pressure; ContSBP = mean of continuously measured systolic blood pressure; Diff. = mean difference.

It is of interest to speculate on the mechanisms behind this tilt-induced pathologic reduction in cardiac output. The identical blood pressure in patients and control subjects suggests that the reduction in cardiac output involves the venous system and dislocation of a greater amount of blood to the lower parts of the body could play a role. Edema is a well-known phenomenon in CRPS that can arise from such venous pooling and may increase after dependency of the affected extremity.⁴² Moreover, the sympathetically mediated vasoconstrictor response during dependency is attenuated in patients with CRPS in the clinically affected and unaffected extremity,⁴³ and there are reports of increased capillary permeability in CRPS.⁴⁴ If the tilt-induced abnormal decrease in cardiac output in the patients was due to regional pooling in the affected extremity, the reduction should be highest in

the patients with an affected lower extremity due to the greater venous system in the legs. This was not the case (data not reported). Thus, if venous pooling is involved, a general rather than a regional venous pooling should be the case. However, we did not control for changes in swelling in the extremities during upright positioning, and peripheral changes in CRPS needs to be tested further.

Five control subjects fainted during tilt and were substituted by five others. Comparing tilt baseline data before and after the exclusion of fainters showed no differences (data not shown). Therefore, the exclusion did not skew the dataset. Tilt-induced syncope is not pathologic but occurs in 10–20% of healthy persons.³⁹ None of the patients with CRPS had syncope during tilt-table testing, which may be due to the exaggerated increase in the total peripheral resistance.

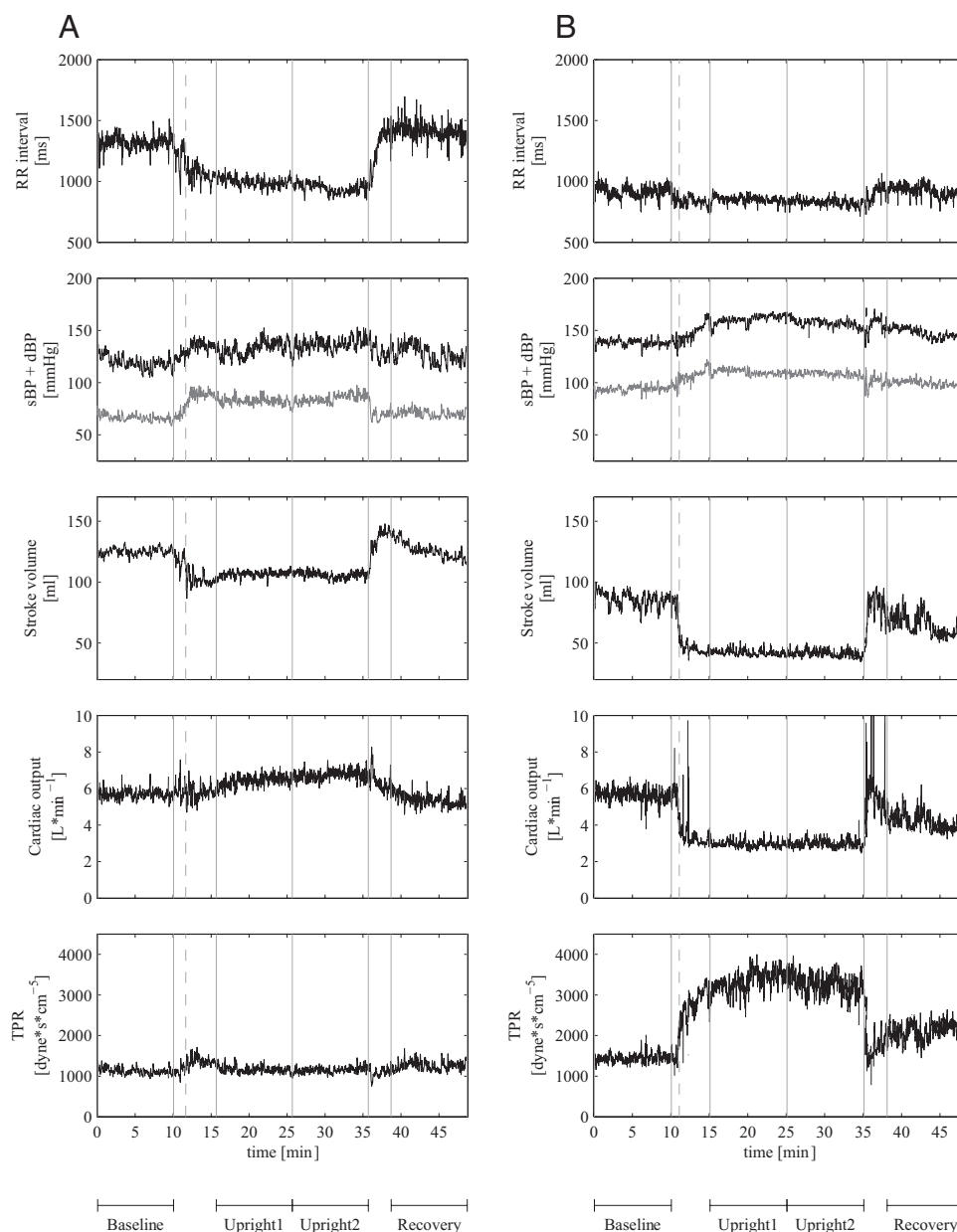


Fig. 2. Orthostatic-induced hemodynamic changes in a healthy control subject (A) and a patient with complex regional pain syndrome (B). Hemodynamic parameters were measured during 10-min supine rest (Baseline), two times 10 min in 60° upright position (Upright1, Upright2), and 10 min supine recovery (Recovery). The broken line marks the initiation of the tilt. In the patient with complex regional pain syndrome (B), the decrease in stroke volume in the upright position was not followed by a compensatory increase in heart rate (reduction in RR intervals) but by a reduction in cardiac output. To avoid decreases in the arterial blood pressure, there was a compensatory exaggerated increase in the total peripheral resistance (TPR) in the upright position. dBP = diastolic blood pressure; ms = milliseconds; RR interval = mean time between consecutive normal R waves in the QRS complexes; sBP = systolic blood pressure.

The inability of the patients to protect their cardiac output during orthostatic stress was not linked to pain intensity but was aggravated with the chronicity of the disease. This finding strongly suggests that the dysfunction of the systemic circulation is a feature of the current pain condition and not related to pain *per se*.

In conclusion, the patients with CRPS were not able to preserve cardiac output during orthostatic stress in comparison with control subjects. These hemodynamic changes may

involve peripheral mechanisms with dislocation of a greater amount of blood to the lower parts of the body.

Reduced Performance of the Arithmetic Stress Test

The PASAT score was lower in patients with CRPS in comparison with control subjects and comparable to values in postconcussion patients. This inability to process information at a normal rate²⁰ could be due to the effects of opioids and sedatives. However, 85% of the patients

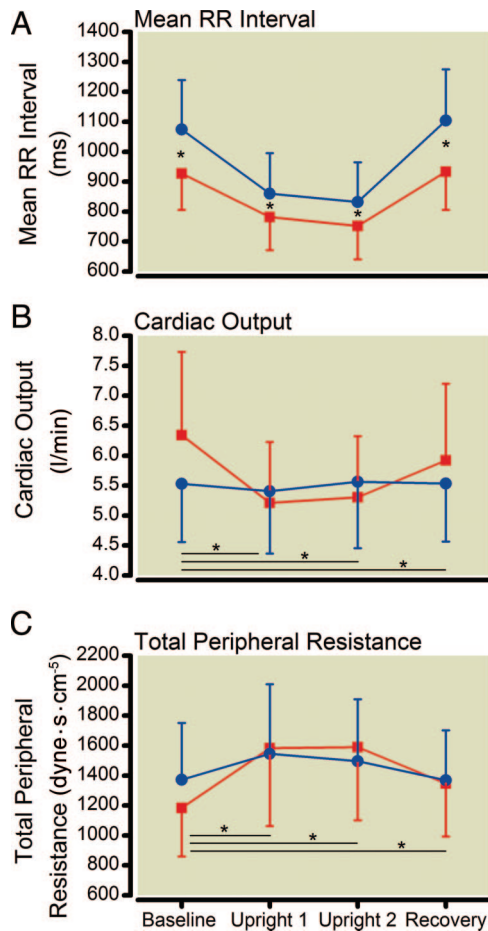


Fig. 3. Effect of tilt-table testing on the mean of all normal RR intervals (mean RR interval), cardiac output, and total peripheral resistance in patients (squares) and control subjects (circles). Hemodynamic parameters were measured during 10 min supine rest (Baseline), two times 10 min in 60° upright position (Upright 1, Upright 2), and 10 min supine recovery (Recovery). For the mean RR interval (A) the main effect of the group was significant with significantly decreased RR interval in patients compared with control subjects during all four conditions. For cardiac output and total peripheral resistance there was a significant condition by group interaction. Patients had a significantly higher reduction in cardiac output (B) and increase in total peripheral resistance (C) compared with control subjects, at the change from supine baseline to upright position. These changes remained significant during the recovery period. Asterisks indicate significant changes. Values in mean (SD). ms = milliseconds; RR interval = mean time between consecutive normal R waves in the QRS complexes.

performed less well than the matched control subjects, including patients who did not receive medical treatment, suggesting that other mechanisms are of importance. The high pain intensity in the patients may have induced chronic stress.⁴⁵ Chronic stress affects the speed of short-term memory⁴⁶ and repeated stress also has an effect on brain function with structural changes of the hippocampus, a brain region that participates in memory and regulates the stress response.⁴⁷

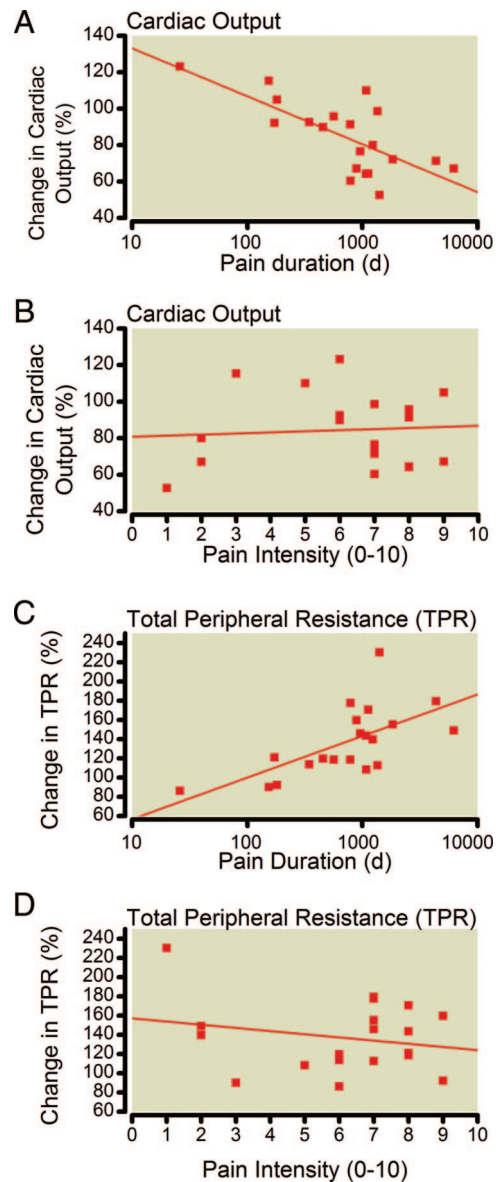


Fig. 4. Pain duration is inversely correlated with tilt-induced reduction in cardiac output (A) and directly correlated with an increase in total peripheral resistance (C). Pain intensity is not correlated to tilt-induced changes in cardiac output (B) or total peripheral resistance (D).

Limitations

It was not possible to match medication status in patients and control subjects. To reduce this source of error, many drugs were avoided in a relevant time interval before the experimental sessions (table 1), and patients taking drugs potentially affecting the vascular or autonomic system were excluded. Hypothyroidism and thyroid hormone replacement therapy may affect the autonomic nervous system but had no effect in the current study, where both a patient and a control subject underwent levothyroxine treatment.

Smoking affects the cardiovascular system, and it would have been preferable to match groups on this variable. Moreover, some patients may have experienced withdrawal from

caffeine or nicotine at the time of the experiment. Participants had at least 12 h smoking abstinence before the experimental sessions, but there may be a longer effect of smoking on heart rate variability.⁴⁸ We corrected for smoking by using repeated-measures ANCOVA with smoking as a covariate. The control group included only two smokers, so the smoking adjustment was mainly based on the data from the patient group. However, the adjustment for smoking did not alter the main conclusion.

The transition from acute pain to CRPS is often insidious and gradual, and it can be difficult to differentiate normal fracture patients⁴⁹ or immobilized subjects¹ from patients with CRPS. Therefore, a pain history shorter than 3 months was used as cutoff. Due to difficulties finding suitable patients for the study, one patient with pain duration of 26 days was included. Although inclusion of this patient represents a deviation from the clinical trials registry this patient still fulfills the research diagnostic criteria for CRPS. Because acute and chronic CRPS may have different autonomic presentations, grouping these two sets of patients may result in loss of useful mechanistic information. In the current study, only one patient had acute CRPS; this finding is unlikely to influence the results. The fact that the hemodynamic dysfunction was aggravated with time does, however, suggest a change in the underlying pathophysiologic mechanisms with time.

Regarding the inability of the patients to preserve cardiac output during upright positioning, additional studies are needed as the changes in hemodynamic parameters are secondary outcome measures, compared in an exploratory way, and not corrected for multiple testing.

Autonomic dysregulation with increased heart rate and reduced heart rate variability has been reported in, for example, fibromyalgia.⁵⁰ Therefore, future studies are needed to examine whether the systemic changes in autonomic function are a cause or a consequence of the CRPS, and whether it is specific to CRPS and the study would have benefited from the inclusion of a group of patients with chronic pain other than CRPS.

Summary

The current CRPS study demonstrated increased heart rate and reduced heart rate variability. The pathologically reduced cardiac output and exaggerated increase in the total peripheral resistance during orthostatic stress point toward a dysfunction of the autonomic control of the cardiovascular system.

The authors thank Michael Vaeth, Ph.D. (Professor, Department of Biostatistics, Aarhus University, Aarhus, Denmark), for statistical advice and Tina Bjerre and Karin Kirketerp (technicians with bachelors degrees in medical laboratory technology, Department of Cardiology, Aarhus University Hospital, Skejby, Denmark) for assisting at the tilt-table testing.

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