

Sympathetic cardiovascular control during orthostatic stress and isometric exercise in adolescent chronic fatigue syndrome

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Abstract The chronic fatigue syndrome (CFS) has been shown to be associated with orthostatic intolerance and cardiovascular dysregulation. We investigated the cardiovascular responses to combined orthostatic stress and isometric exercise in adolescents with CFS. We included a consecutive sample of 15 adolescents 12–18 years old with CFS diagnosed according to a thorough and standardized set of investigations, and a volunteer sample of 56 healthy control subjects of equal sex and age distribution. Heart rate, systolic, mean and diastolic blood pressure, stroke index, and total peripheral resistance index were non-invasively recorded during lower body negative pressure (LBNP) combined with two consecutive periods of handgrip. In addition, we measured baseline plasma catecholamines, and recorded symptoms. At rest, CFS patients had higher heart rate, diastolic blood pressure, plasma norepinephrine ($P < 0.01$), mean blood pressure and plasma epinephrine ($P < 0.05$) than controls. During LBNP, CFS patients had a greater increase in heart rate, diastolic blood pressure, mean blood pressure ($P < 0.05$) and total peripheral resistance index (n.s.) than controls. During handgrip, CFS patients had a smaller increase in heart rate, diastolic blood pressure

($P < 0.05$), mean blood pressure and total peripheral resistance index (n.s.) than controls. Our results indicate that adolescents with CFS have increased sympathetic activity at rest with exaggerated cardiovascular response to orthostatic stress, but attenuated cardiovascular response when performing isometric exercise during orthostatic stress. This suggests that CFS might be causally related to sympathetic dysfunction.

Keywords Sympathetic nervous system · Adolescents · Chronic fatigue syndrome · Hemodynamics · Catecholamines

Introduction

The chronic fatigue syndrome (CFS) is a disabling disease, mainly affecting adolescents and young adults (Prins et al. 2006). The etiology is unknown, but recent evidence suggests that cardiovascular dysregulation may play an important role. Various forms of orthostatic intolerance have been demonstrated both in adult (Bou-Holaigah et al. 1995; Peckerman et al. 2003a) and pediatric (Rowe et al. 1995; Stewart et al. 1999; Wyller et al. 2007a) patients, as well as abnormalities in cerebral (Tanaka et al. 2002), muscle (McCully et al. 2004), and skin (Wyller et al. 2007b) hemodynamics. Dysfunction of the autonomic nervous system, and particularly the sympathetic branch, has therefore been proposed as an important component of the pathophysiology (Freeman and Komaroff 1997). The aim of this study was to explore the pathophysiology of CFS further by a detailed study of cardiovascular adjustments to orthostatic stress and isometric exercise.

The technique of lower body negative pressure (LBNP) is a well-established tool for studies of cardiovascular

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adjustments during orthostatic stress (Stevens and Lamb 1965). Indirectly, the test also yields information on the underlying neural reflex loops originating from cardiopulmonary and arterial baroreceptors. Compared to other tests of orthostasis, LBNP has the advantage of being more accurate because the subjects do not move and the effect of the muscle venous pump is eliminated. As far as we know, this technique has not been previously used in a CFS study.

Handgrip is a common test for studies of cardiovascular adjustments during isometric exercise (Goodwin et al. 1972). During handgrip, the cardiovascular adjustments are mainly due to a “central command” in the brain causing a gradual increase in the set point of the barostat, thereby enhancing sympathetic neural activity. Thus, handgrip is quite different from LBNP in terms of autonomic neural activity, and should therefore yield additional insight into the pathophysiology of CFS.

Sophisticated experimental methods often have the disadvantage of being far from patients’ real life experiences, thereby reducing their validity. In CFS patients, both fatigue and other symptoms are worsened by ordinary daily activities like dressing, housework etc (Prins et al. 2006; Fukuda et al. 1994). These activities involve upright posture in combination with both isometric and dynamic muscular work of varying intensity. In an attempt to mimic partly the physical stressors of real life, we decided to study the cardiovascular adjustments to LBNP (orthostatic stress) and handgrip (isometric exercise) in combination, thus exploring whether autonomic dysfunction could be directly linked to patients’ complaints. To our knowledge, such a combined approach has never been applied to the study of CFS pathophysiology.

Materials and methods

Subjects

CFS patients 12–18 years old were consecutively recruited from the outpatient clinic at the Department of Pediatrics, Rikshospitalet-Radiumhospitalet Medical Centre, Oslo, Norway, serving as a national referral center for children and adolescents with unexplained chronic fatigue. Other disease states that might explain their present symptoms, such as autoimmune, endocrine, neurologic or psychiatric disorders, were ruled out by a thorough and standardized set of investigations. Different case definitions of CFS exist. This study used a slight modification of the definition from the Centers for Disease Control and Prevention (CDC), in which the main criterion are at least 6 months of chronic or relapsing fatigue, severely affecting daily activities (Fukuda et al. 1994). In addition, according to the CDC-definition, patients should report at least four of eight specific accom-

panying symptoms. However, the validity of this last demand has been questioned (Cho et al. 2006), particularly in the pediatric population (Franklin 1998), and accompanying symptoms were not required in this study.

Healthy controls 12–18 years volunteered from local schools. In order to increase the statistical power, we strived towards a 1:4 relation between patients and controls. Through our communication with the responsible teachers, we established a recruiting process that assured an equal distribution of age and sex among the two groups. Subjects having a chronic disease (such as allergy) or using drugs (including contraceptive pills) on a regular basis were excluded.

One week prior to the experiments, all participants were instructed not to drink beverages containing alcohol or caffeine, not to take any drugs, and not to use tobacco products. On the day of the experiments, they were supposed to have fasted overnight.

Written, informed consent was obtained from all participants and their parents. The study was approved by the Regional committee for ethics in medical research.

Questionnaire

Items from the Autonomic Symptom Profile, a validated instrument for assessing orthostatic intolerance and other variants of autonomic dysfunction (Suarez et al. 1999), was translated into Norwegian by one of the authors (VBW) and slightly modified in order to fit our particular age group. Five items were combined to produce an ordinal scale (range 0–5) for grading of orthostatic symptom severity. Based on personal clinical experience with CFS-patients, we added questions focusing on functional consequences of this disease. The subjects answered by interview.

Catecholamines

Experiments started at 8 a.m. The subjects were supposed to have applied an ointment containing the local anesthetic lidocaine (Emla[®]) on the skin in the elbows 1 h in advance. They rested supine for about 15 min, whereupon a catheter was placed in an antecubital vein. After supine rest for another 15 min, plasma samples were collected on ice cold glutathione-EGTA tubes. Catecholamine concentrations were assayed by high performance liquid chromatography (HPLC) with a reverse phase column and glassy carbon electrochemical detector (Agilent Technologies, CO, USA), using a commercial kit (Chromsystems, München, Germany).

Lower body negative pressure with handgrip

Experiments started at 11 a.m. The participants had been offered a light meal (1–2 pieces of bread, 1 glass of juice)

2 h before, but were otherwise not allowed to eat or drink. They lay supine with their lower body in a plastic chamber, in which air could be evacuated very rapidly, thus reaching a pre-defined negative pressure within milliseconds (Hisdal et al. 2003). In order to prevent air leak, rubber devices were used to make a tight seal around the subjects' waist. They were lightly dressed, and the ambient temperature was kept between 23 and 26°C. They were familiarized with the test situations in two pilot experiments.

By means of an electronic device (AB-detector, Gøteborg, Sweden), the force of the subjects' left-sided handgrip was continuously displayed to them. They were first asked to perform maximum isometric work for about 10 s. Based on the mean value, the 30% level was calculated, and they were then asked to use a couple of minutes to familiarize with this force.

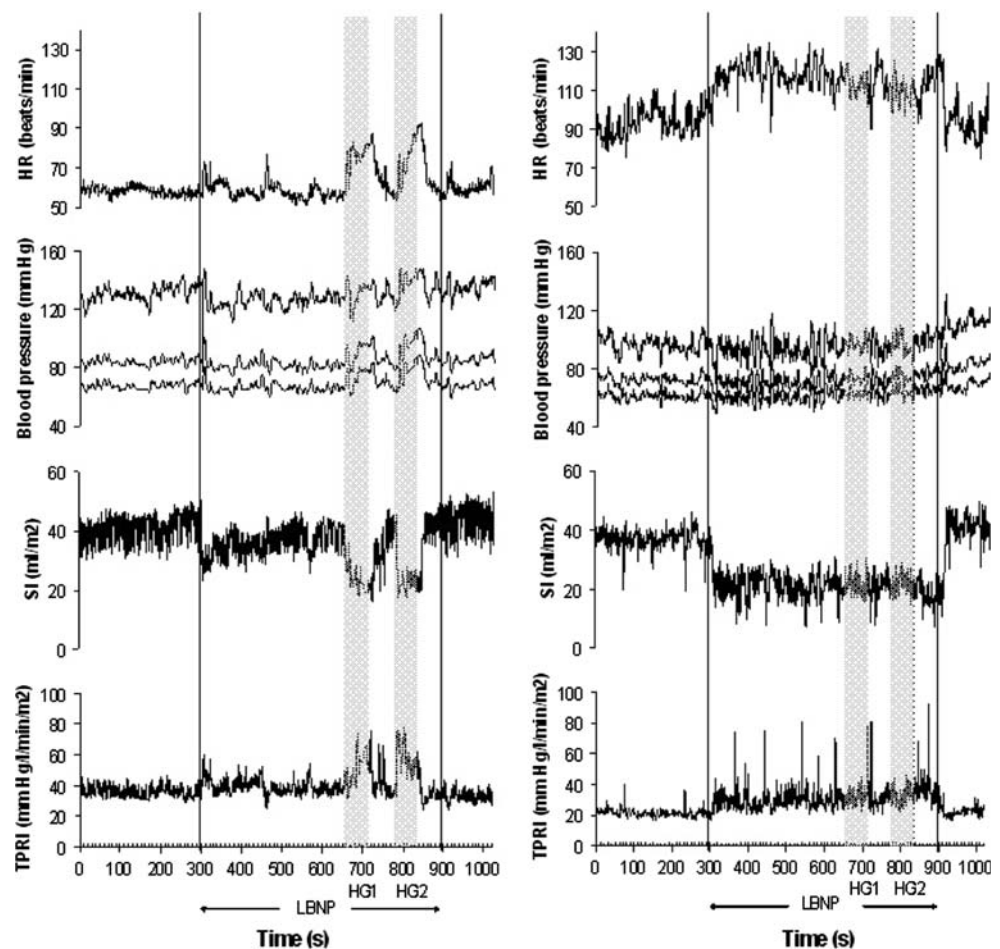
Five minutes were used for baseline registration of cardiovascular variables. Then, LBNP of -20 mm Hg was applied instantaneously. After 6 min of LBNP, the subjects were asked to perform left-sided handgrip with 30% of maximum force for one minute (HG1). They relaxed during the next minute, and then repeated handgrip with identical force and duration (HG2). One minute after termination of

HG2, LBNP was turned off instantaneously. However, registration continued for another two minutes, making the total experimental period 17 min (Fig. 1).

In two subjects (one CFS patient, one control), only one complete run of LBNP and handgrip was performed, due to dizziness or other unpleasant experience. In all other subjects, the experiment was repeated once.

Instantaneous heart rate (HR) was obtained from the R–R interval of the ECG. Photoplethysmography on the right middle finger was used to obtain a non-invasive, continuous recording of arterial blood pressure (2300 Finapres, Ohmeda, Madison, WI, US). This method correlates satisfactorily with invasive pressure measurements (Parati et al. 1989), and has also been validated in adolescents and children (Seifer and Kenny 2001). Continuous recording of maximum blood flow velocity in the ascending aorta was obtained by a bidirectional ultrasound Doppler velocimeter (SD-100, GE Vingmed Ultrasound, Horten, Norway), operating in pulsed mode at 2 MHz. By a handheld transducer, the ultrasound beam was directed from the suprasternal notch towards the aortic root. The sample volume range was adjusted so that measurements were made 1–2 cm above the aortic valve.

Fig. 1 Original recordings of cardiovascular data from one control (*left*) and one CFS patient (*right*) during lower body negative pressure (LBNP) with handgrip. Artifacts in the records have been manually removed by linear interpolation. HR heart rate, SI stroke index, TPRI total peripheral resistance index, HG1 handgrip 1, HG2 handgrip 2



All recorded signals, including the pressure in the LBNP-chamber and the force of the handgrip, were on-line transferred to a recording computer running a program for real-time data acquisition (developed by Morten Eriksen, Department of Physiology, University of Oslo, Oslo, Norway). In a separate session, the diameter of the aortic valve orifice was determined by 2D ultrasound imaging, and used to calculate the area of the orifice. Beat-to-beat stroke volume (SV) was then calculated by multiplying the value obtained by numerical integration of the recorded instantaneous maximal blood flow velocity in the ascending aorta during each R–R interval by the area of the orifice. This method has been validated in a previous study (Eriksen and Walloe 1990). Beat-to-beat mean arterial blood pressure (MBP) was similarly calculated by numerical integration of the recorded instantaneous blood pressure.

Data were exported to Microsoft Excel for further calculations. Beat-to-beat stroke index (SI) was obtained by dividing SV by body surface area (BSA), estimated from the subjects' height and weight. Beat-to-beat total peripheral resistance index (TPRI) was calculated as MBP divided by the product of SI and HR.

Data analysis

For each experimental run of LBNP with handgrip, the median value of all cardiovascular variables were calculated in the following time intervals: 260–290 s [Pre LBNP (baseline)], 620–650 s (Pre HG1), 715–718 s (Max HG1), 740–770 s (Pre HG2), 835–838 s (Max HG2), 980–1,010 s (Post LBNP). Delta LBNP (Pre HG1–Pre LBNP), Delta HG1 (Max HG1–Pre HG1), and Delta HG2 (Max HG2–Pre HG2) were also computed for each variable. The short (3 s) time interval for handgrip calculations were chosen in order to obtain the most extreme (maximal) responses in each individual. We thereafter computed the arithmetical mean for each subject in each time interval, and the mean for the two groups.

In order to visualize the transient changes in cardiovascular variables at the beginning of LBNP and during HG1 (Figs. 2, 3), relevant parts of the recording of each experimental run were converted to 4 Hz time series of equal length by linear interpolation. The time series were filtered by assigning the median value within a 5 s sliding window to each time point, thus removing both minor artifacts and normal high-frequency variability. Remaining artifacts in the records were removed manually by linear interpolation. All time series were normalized, taking the mean value of the first time period as zero. Coherent averaging was then performed by calculating the arithmetical mean for each time point (Rompelman and Ros 1986).

The statistical analyses were carried out using SPSS statistical software. Based upon inspection of plots, cardiovas-

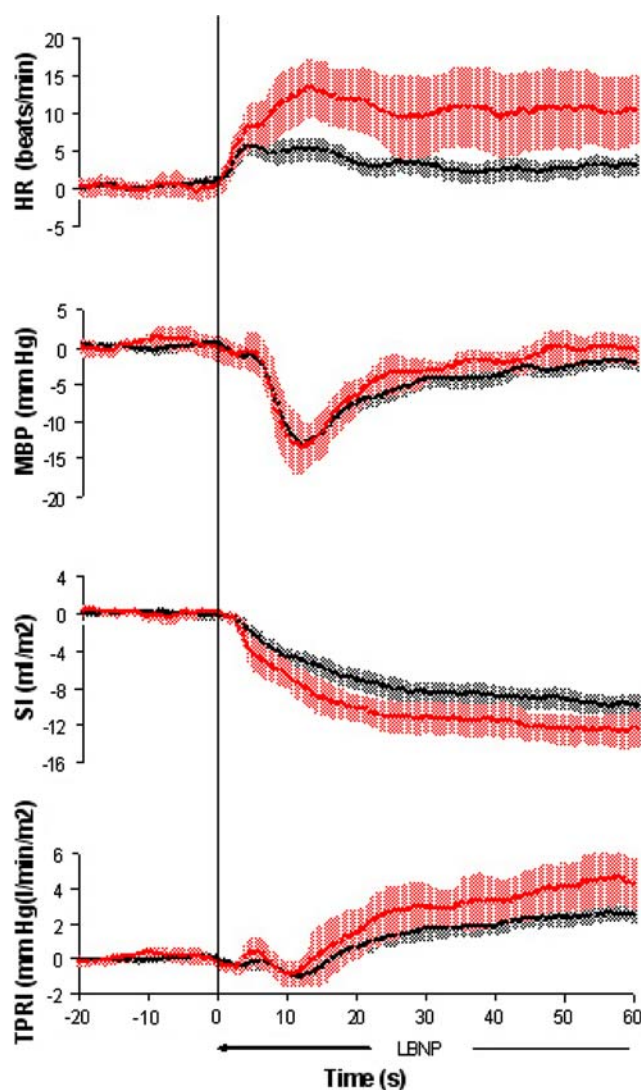


Fig. 2 Mean changes in cardiovascular variables (based upon coherent averaging of individual recordings) in controls (*black*) and CFS-patients (*red*) during the first minute of lower body negative pressure (LBNP). The differences between the two groups illustrated in this figure are representative for the entire LBNP-period prior to handgrip 1. Shaded areas represent 95% confidence intervals for the mean (shown for clarity, although the consecutive data points are not independent of each other). Data are normalized to zero for the first time period. The time-axis is adjusted so that zero corresponds to LBNP on. *HR* heart rate, *MBP* mean blood pressure (from Finapres), *SI* stroke index, *TPRI* total peripheral resistance index

cular and catecholamine variables were appraised to follow an approximate normal distribution. However, due to the presence of occasional outliers, we used non-parametric tests (2-sided) to explore differences between the two groups. A $P \leq 0.05$ was considered statistically significant. In order to reduce the methodological problem of multiple comparisons, statistical tests were only performed for the cardiovascular variables Pre LBNP, Delta LBNP and Delta HG1 (Table 4). Among these variables, the changes in HR

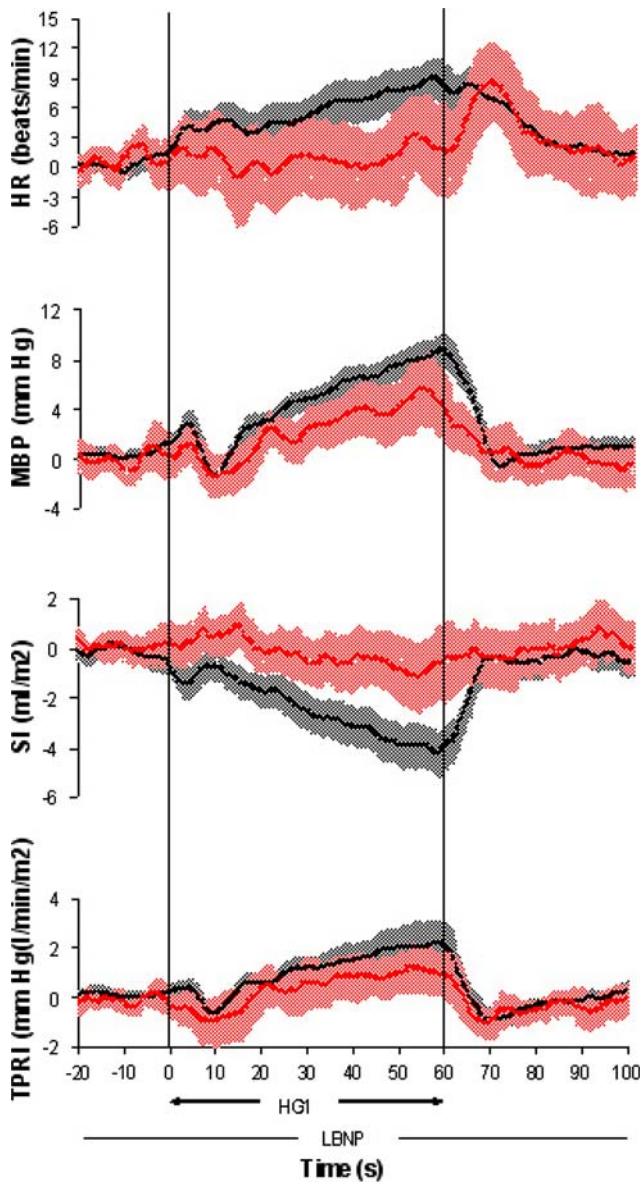


Fig. 3 Mean changes in cardiovascular variables (based upon coherent averaging of individual recordings) in controls (black) and CFS-patients (red) at handgrip 1 (HGI). Lower body negative pressure (LBNP) is applied during the whole period. Shaded areas represent 95% confidence intervals for the mean (shown for clarity, although the consecutive data points are not independent of each other). Data are normalized to zero for the first time period. The time-axis is adjusted so that zero corresponds to start of isometric exercise. HR heart rate, MBP mean blood pressure (from Finapres), SI stroke index, TPRI total peripheral resistance index

and DBP were considered most central to our hypothesis of cardiovascular dysregulation.

Results

A total of 15 CFS patients and 56 healthy controls were included in the study (Table 1). The two groups were

Table 1 Subject characteristics

| | Control (n = 56) | Chronic fatigue (n = 15) |
|-------------------------------------|------------------|--------------------------|
| Female gender | | |
| n | 33 | 10 |
| % | 58.9 | 66.7 |
| Age (years) | 15.6 (13–18) | 15.1 (12–18) |
| Weight (kg) | 61.6 (44–99) | 59.1 (43–92) |
| Height (cm) | 171.5 (149–195) | 171.4 (160–192) |
| Body surface area (m ²) | 1.7 (1.4–2.2) | 1.7 (1.4–2.2) |
| Duration of fatigue (months) | | 31.1 (6–60) |

Mean values (range)

Table 2 Questionnaire results

| | Control ^a | | Chronic fatigue ^a | |
|--|----------------------|------|------------------------------|--------------------|
| | n | % | n | % |
| Orthostatic symptoms | | | | |
| Having experienced faint when rising quickly | 4 | 8.2 | 4 | 26.7 |
| Feeling dizzy just after a heavy meal | 3 | 6.1 | 3 | 20.0 |
| Feeling dizzy after standing upright for a long period | 11 | 22.4 | 10 | 66.7 [†] |
| Feeling dizzy during moderate physical exercise | 19 | 38.8 | 13 | 92.9 [‡] |
| Feeling dizzy taking a hot bath or shower | 11 | 22.4 | 8 | 53.3 [§] |
| Functional consequences | | | | |
| School absence more than once a week | 0 | 0.0 | 10 | 77.0 [‡] |
| Absence from leisure activities more than once a week | 0 | 0.0 | 13 | 100.0 [‡] |
| Permanently bedridden | 0 | 0.0 | 0 | 0.0 |

^a The questionnaire was revised during the study period. Therefore, the totals vary from item to item

[†] P ≤ 0.01 compared with controls, Fisher’s exact test

[‡] P ≤ 0.001 compared with controls, Fisher’s exact test

[§] P ≤ 0.05 compared with controls, Fisher’s exact test

comparable regarding sex, age, weight and height. All were of Caucasian ethnicity, except one control. Nine controls (16%) performed physical exercise 10 h/week or more. None of the controls reported receiving psychological treatment.

Mean duration of fatigue among the patients was 31 months. They had experienced significantly more orthostatic faints than controls, and a majority reported dizziness during standing, physical exercise, and showering/bathing (Table 2). The functional impairments were severe; the patients were physically inactive, did not participate in leisure activities and had a high level of school absence. However, no one was permanently bedridden.

At rest, the CFS patients had significantly higher levels of plasma catecholamines (Table 3), and significantly

Table 3 Plasma concentrations of catecholamines

| | Control ^a | Chronic fatigue ^a |
|-------------------------|---------------------------------------|--|
| Norepinephrine (pmol/L) | 1,265 (1,129–1,401) [392–1,898] | 1,664 [†] (1,448–1,881) [926–2,621] |
| Epinephrine (pmol/L) | 171 (153–189) [62–388] | 229 [‡] (182–276) [114–399] |

Mean (95% confidence interval) [range]

^a Blood samples were not obtained from three controls due to technical difficulties

[†] $P \leq 0.01$ compared with controls, Wilcoxon–Mann–Whitney’s test

[‡] $P \leq 0.05$ compared with controls, Wilcoxon–Mann–Whitney’s test

higher HR, MBP and DBP (Table 4) than controls. CFS patients also had lower SI, but the differences were not statistically significant. SBP and TPRI were similar in the two groups.

In the Pre HG1-period, when LBNP was applied, the CFS patients had a more pronounced increase in HR, MBP and DBP than controls, thus enhancing the differences already present at baseline (Table 4; Figs. 1, 2). SI simultaneously decreased to a lower level in the CFS patients. The increase in TPRI was also greater in the CFS patients, but the differences were not statistically significant.

During HG1, the increase in HR and DBP, and the decrease in SI, were significantly less in CFS patients than in controls, thus reducing the differences between the two groups (Table 4; Fig. 3). MBP and TPRI also increased less in CFS patients than in controls, but the differences were not statistically significant. The mean (confidence interval) force generation during handgrip was 59.8 (51.8–67.9) N among controls and 37.6 (25.1–50.1) N among CFS patients.

In the Pre HG2-period, all variables in both groups returned to levels similar to those observed during pre HG1 (Fig. 3). During HG2, changes similar to those during HG1 were observed, although less pronounced. Post LBNP, all variables in both groups returned to levels similar to those observed pre LBNP.

In the CFS patients, there were no significant correlations between orthostatic symptom severity scale and the mean values of HR and DBP for delta LBNP, delta HG1, and delta HG2 (Kendall’s Tau-b).

Discussion

The most important findings in this study are: (1) CFS patients have more orthostatic symptoms than controls. (2) At rest, the CFS patients had higher levels of catecholamines, and higher HR, MBP and DBP than controls. (3)

During orthostatic stress (LBNP), the CFS patients had a greater increase in HR, MBP and DBP, and a greater decrease in SI, than controls. (4) When performing isometric exercise (handgrip) during orthostatic stress, the CFS patients had a smaller increase in HR and DBP, and a smaller decrease in SI, than controls. Taken together, the findings demonstrate that CFS patients have significantly abnormal hemodynamic responses to experimental activities that mimic daily life, suggesting a link between cardiovascular dysregulation and the patients’ subjective complaints of orthostatic symptoms.

Observations at rest

Our baseline data are similar to observations made in adult CFS patients (Peckerman et al. 2003a; LaManca et al. 1999), and indicate a general sympathetic activation.

Observations during orthostatic stress

Moderate levels of LBNP have a significant effect on central blood volume, activating the cardiopulmonary baroreceptor reflex (Triedman et al. 1993). The normal result is a sympathetically mediated increase in TPRI combined with augmented sympathetic control of the SA-node, even though HR does not necessarily increase with low levels of LBNP. Recent evidence suggests that arterial baroreceptor reflexes are also activated in this situation (Hisdal et al. 2001).

Our observations of a pronounced increase of HR, MBP and DBP in the CFS patients during LBNP, as well as a tendency towards higher TPRI, indicate an enhanced sympathetic response to orthostatic stress. The pronounced HR-increase has been reported by others using head-up tilt or similar orthostatic tests, in adult as well as in pediatric populations (Bou-Holaigah et al. 1995; Peckerman et al. 2003a; Rowe et al. 1995; Stewart et al. 1999; Freeman and Komaroff 1997; Wyller et al. 2007a). The reports of blood pressure responses are more conflicting. For instance, Freeman and Komaroff found an enhanced decline of DBP in CFS patients during 60° head-up tilt, whereas we observed an increase during LBNP. Likewise, Stewart et al. reported a fall of SBP in adolescent CFS patients during head-up tilt, whereas our patients did not differ from controls during LBNP. These apparent contradictions may be explained by the different test procedures.

One possible explanation for the findings in this study is that CFS patients have moderate hypovolemia at baseline, which significantly alters the response to LBNP. Comparing hypovolemic adults with controls, Kimmerly and Shoemaker (2002) reported a greater increase in both HR and MBP during LBNP –20 mm Hg, similar to our observations. Central hypovolemia in CFS could be due to increased

Table 4 Cardiovascular variables during LBNP with handgrip

| | Pre LBNP (baseline) | | | Delta LBNP | | | Max HG1 | | | Delta HG1 | | |
|------------------------------------|--|---|--|--|--|---|--|---|------------------------------------|------------------------------------|--|--|
| | Control | Chronic fatigue | Control | Chronic fatigue | Control | Chronic fatigue | Control | Chronic fatigue | Control | Chronic fatigue | Control | Chronic fatigue |
| HR (beats/min) | 65.7 (62.8–68.6) [40.5–88.5] | 75.8 [†] (69.1–82.6) [55.1–98.8] | 72.3 (68.3–76.2) [44.0–107.5] | 88.2 (82.2–94.3) [73.3–113.1] | 6.6 (4.8–8.4) [–4.4–24.1] | 12.4 [‡] (8.3–16.5) [1.7–25.8] | 81.2 (77.3–85.1) [51.9–108.4] | 90.8 (86.8–94.8) [79.8–101.2] | 8.9 (6.7–11.2) [–3.1–35.2] | 8.9 (6.7–11.2) [–3.1–35.2] | 2.6 [‡] (–2.0–7.1) [–12.7–23.4] | 2.6 [‡] (–2.0–7.1) [–12.7–23.4] |
| SBP (mm Hg) ^a | 119.3 (115.0–123.5) [89.4–164.0] | 119.5 (111.9–127.1) [102.5–153.1] | 118.5 (114.7–122.3) [86.5–158.6] | 121.0 (112.7–129.3) [96.9–147.1] | –0.8 (–2.9–1.4) [–18.6–19.8] | 1.5 (–3.2–6.2) [–11.0–14.6] | 124.7 (120.8–128.6) [82.5–158.4] | 127.0 (117.0–137.0) [105.1–172.1] | 6.2 (4.0–8.4) [–9.4–33.4] | 6.2 (4.0–8.4) [–9.4–33.4] | 6.0 (0.8–11.2) [–8.3–25.0] | 6.0 (0.8–11.2) [–8.3–25.0] |
| MBP (mm Hg) ^a | 80.3 (78.1–82.5) [66.0–105.3] | 84.6 [‡] (81.2–87.9) [75.9–92.6] | 81.4 (79.4–83.5) [68.4–100.7] | 87.9 (83.9–91.9) [75.8–99.4] | 1.1 (0.1–2.1) [–5.4–14.9] | 3.3 [‡] (1.3–5.4) [–3.1–8.4] | 89.6 (87.0–92.1) [70.1–120.8] | 93.4 (88.8–98.1) [80.1–111.8] | 8.1 (6.7–9.6) [0.8–30.0] | 8.1 (6.7–9.6) [0.8–30.0] | 5.5 (2.4–8.6) [–1.6–19.7] | 5.5 (2.4–8.6) [–1.6–19.7] |
| DBP (mm Hg) ^a | 65.0 (63.1–67.0) [52.6–86.9] | 70.1 [†] (67.2–73.1) [63.0–79.3] | 67.2 (65.3–69.1) [55.7–87.4] | 74.9 (71.7–78.1) [65.8–83.7] | 2.2 (1.2–3.1) [–5.2–14.8] | 4.8 [‡] (2.8–6.7) [–0.4–11.2] | 75.6 (73.1–78.1) [60.4–109.4] | 80.2 (76.7–83.6) [68.1–90.3] | 8.4 (6.9–9.9) [–0.8–29.5] | 8.4 (6.9–9.9) [–0.8–29.5] | 5.3 [‡] (2.6–7.9) [–0.5–18.2] | 5.3 [‡] (2.6–7.9) [–0.5–18.2] |
| SI (ml/m ²) | 41.3 (39.1–43.5) [22.4–62.7] | 37.4 (32.9–41.8) [25.4–52.0] | 31.2 (29.3–33.1) [16.6–47.5] | 25.5 (21.6–29.5) [16.3–40.0] | –10.1 (–11.5––8.7) [–24.8– –1.0] | –11.8 (–14.1––9.5) [–20.3––6.0] | 27.0 (25.1–28.9) [16.1–42.8] | 24.9 (20.5–29.3) [14.9–42.4] | –4.2 (–5.3––3.2) [–16.6–1.7] | –4.2 (–5.3––3.2) [–16.6–1.7] | –0.6 [§] (–2.1–0.9) [–6.7–3.5] | –0.6 [§] (–2.1–0.9) [–6.7–3.5] |
| TPRI (mm Hg/l/min/m ²) | 11.1 (10.1–12.1) [5.2–21.2] | 11.6 (9.9–13.2) [7.8–17.4] | 13.8 (12.5–15.0) [6.3–28.3] | 15.4 (12.8–18.1) [9.1–23.8] | 2.7 (2.2–3.2) [–0.4–7.3] | 3.9 (2.5–5.3) [0.6–8.8] | 16.0 (14.0–17.9) [6.7–55.6] | 16.5 (13.7–19.3) [9.9–27.1] | 2.2 (1.1–3.3) [–1.8–27.3] | 2.2 (1.1–3.3) [–1.8–27.3] | 1.1 (0.0–2.1) [–1.6–4.6] | 1.1 (0.0–2.1) [–1.6–4.6] |

Mean (95% confidence interval) [range]. In order to reduce the methodological problem of multiple comparisons, statistical tests were only performed for the cardiovascular variables Pre LBNP, Delta LBNP and Delta HG1. HR heart rate, SBP systolic blood pressure, MBP mean blood pressure, DBP diastolic blood pressure, SI stroke index, TPRI total peripheral resistance index

^a Finapress finger blood pressure

[†] $P \leq 0.01$ compared with controls, Wilcoxon-Mann-Whitney's test

[‡] $P \leq 0.05$ compared with controls, Wilcoxon-Mann-Whitney's test

[§] $P \leq 0.001$ compared with controls, Wilcoxon-Mann-Whitney's test

venous compliance. Supporting this hypothesis, Streeten (2001) has provided evidence of sympathetic denervation of lower limb veins in CFS patients. A more pronounced reduction in SI during orthostatic stress, a phenomenon also reported by others (Peckerman et al. 2003a; LaManca et al. 1999), is consistent with hypovolemia as well. However, this observation can be explained entirely by reduced filling time due to increased HR (Elstad et al. 2001).

An alternative explanation for the observed response to LBNP is an abnormality in the cardiopulmonary and/or arterial baroreceptor reflexes, either due to changes in afferent or efferent neural pathways, or changes in the brainstem cardiovascular control center. An enhanced decline in the arterial baroreceptor-sensitivity during standing has been demonstrated in adult CFS patients (Peckerman et al. 2003b), and similar results have been reported in adolescents (Stewart 2000). However, the integrity of the cardiopulmonary reflex loop has not been specifically investigated.

A third possibility is deconditioning due to prolonged inactivity. Importantly, reduced blood volume, occurring within days, is a key feature in this process (Fortney et al. 1996). However, cardiac remodeling and changes in sympathetic nerve function—which are slower processes—may also contribute to the orthostatic intolerance after long-lasting exposure to microgravity (Perhonen et al. 2001). The amount of gravitational stimuli necessary to prevent deconditioning, remains a question of debate. Butler et al. demonstrated significant, but quickly reversible effects of 4-h head-down tilt (Butler et al. 1991). However, most studies addressing this topic have exposed the subjects to a very strict bed-rest regimen lasting weeks or months. Evidence from both animal and human studies suggests that intermittent exposure to gravity during a bed-rest period is sufficient to prevent deconditioning (Sun et al. 2003; Zhang et al. 2000). As none of our CFS patients were permanently bedridden, it is unlikely that deconditioning alone can explain the results.

Observations during isometric exercise

During isometric exercise, there is a general enhancement of sympathetic neural activity increasing both HR and TPRI, and gradually elevating arterial blood pressure (Goodwin et al. 1972). The underlying mechanism for this response is probably a “central command” in the brain, eventually combined with activation of reflexes related to metaboreceptors in the working muscle. Evidence indicates that these cardiovascular responses are independent of muscle mass, but depend upon the relative tension of the contraction (Williams 1991).

Our observation of an attenuated increase in HR, blood pressure and TPRI during combined LBNP and handgrip

in CFS patients might indicate a reduced sympathetic response to isometric exercise. The CFS patients produced significantly less force during handgrip than normal controls, and one possible explanation for the hemodynamic differences is simply that the CFS patients did not reach 30% of their maximum handgrip capacity.

However, the difference in force generation among the two groups could also be due to reduced muscle mass (e.g. related to inactivity) in the CFS patients. If the patients did reach 30% of their maximum handgrip capacity, their reduced response could indicate abnormalities of the efferent sympathetic pathways, including disturbances of norepinephrine release and/or reuptake. Interestingly, such disturbances have been documented in the postural orthostatic tachycardia syndrome (POTS), and a strong relation between POTS and CFS has been established in adults (Farquhar et al. 2000) as well as adolescents (Stewart 2000). In a detailed study of adult POTS-patients, Jacob et al. found reduced norepinephrine reuptake in the sympathetic synapse (Jacob et al. 1999), and a mutation in the norepinephrine reuptake protein was indeed documented in a pair of twins suffering from POTS (Shannon et al. 2000). Whether reduced norepinephrine reuptake can be demonstrated in CFS patients as well, should be a subject for further research.

Alternatively, a reduced sympathetic response might be explained from disturbances of “central command”. Recent electrophysiologic experiments in CFS patients have revealed reduced activity in motor neurons and altered EEG-signals during voluntary isometric exercise, pointing towards diminished activation from the central nervous system (Schillings et al. 2004).

Finally, reduced responsiveness among CFS patients might be a consequence of their exaggerated response to LBNP. However, previous experiments from our own laboratory indicate that moderate orthostatic stress exerts only a limited influence on the cardiovascular adjustments during isometric exercise (Hisdal et al. 2004).

Clinical relevance

The high prevalence of orthostatic symptoms in CFS patients (Peckerman et al. 2003a; Stewart et al. 1999), also documented in this study, directly suggests a link between cardiovascular dysregulation and patients’ complaints. The clinical relevance of our findings is further strengthened by the strikingly homogenous responses within the patient group, creating significant differences from controls despite a small number of subjects studied. However, correlation analyses failed to demonstrate significant relations between orthostatic symptoms severity score and selected cardiovascular variables. This might be explained by low validity of our questionnaire.

Long-lasting sympathetic overactivity may have detrimental effects at the tissue level promoting increased oxidative stress (Dhalla et al. 2000), which in fact has been reported among CFS patients (Kennedy et al. 2005). Thus, sympatholytic drugs may constitute a possible treatment approach. Indeed, we have reported tremendous effect of the non-selective beta-blocker propranolol in one CFS patient (Wyller et al. 2007c)

Study limitations

Blood pressures were recorded using the Finapres finger technique only, which is less reliable than ordinary brachial blood pressure measurements. Plasma catecholamines were not measured during LBNP, but could have strengthened our hypothesis of enhanced sympathetic response to orthostatic stress. Neither did we measure blood volume/plasma volume at baseline, leaving the question of hypovolemia in CFS patients unresolved. The force generation and cardiovascular adjustments during isometric exercise were not studied in isolation. Thus, we are unable to tell whether or not orthostatic stress is a prerequisite for the observation of reduced sympathetic response during handgrip in the CFS group. In addition, long-lasting metabolic changes in the muscles during HG1 might have influenced the cardiovascular responses during HG2. Finally, we have only studied 15 CFS patients, reducing the statistical power and questioning the generalizability of our results.

Conclusion

Taken together, our results suggest that CFS patients suffer from a more comprehensive disturbance of sympathetic cardiovascular regulation than previously acknowledged, supporting the hypothesis that dysautonomia may be a central etiologic component of CFS (Freeman and Komaroff 1997). Specifically, the sympathetic nervous system is more activated at rest, and seems to have an enhanced response to orthostatic stress, but has a reduced response to the addition of isometric exercise. These abnormalities may account for the high prevalence of orthostatic symptoms among CFS patients.

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