Enhanced Vagal Withdrawal During Mild Orthostatic Stress in Adolescents with Chronic Fatigue

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Background: Hemodynamic abnormalities have been documented in the chronic fatigue syndrome (CFS), indicating functional disturbances of the autonomic nervous system responsible for cardiovascular regulation. The aim of this study was to investigate autonomic heart rate control during mild orthostatic stress in adolescents with CFS.

Methods: A total of 14 CFS patients and 56 healthy controls having equal distribution of age and gender underwent lower body negative pressure (LBNP) of 20 mmHg. The RR interval (RRI) was recorded continuously, and spectral power densities were computed in the low-frequency (LF) band (0.04–0.15 Hz) and the high-frequency (HF) band (0.15–0.50 Hz) from segments of 120-second length, using an autoregressive algorithm. In addition, the time-domain indices SDNN, pNN50, and r-MSSD were computed.

Results: At rest, CFS had lower RRI than controls ($P < 0.05$), but indices of variability were similar in the two groups. During LBNP, compared to controls, CFS patients had lower normalized and absolute HF power and r-MSSD ($P < 0.05$), and higher RRI ($P < 0.001$), normalized LF power and LF/HF ($P < 0.05$).

Conclusions: During mild orthostatic stress, adolescents with CFS appear to have enhanced vagal withdrawal, leading to a sympathetic predominance of heart rate control compared to controls. Possible underlying mechanisms include hypovolemia and abnormalities of reflex mechanisms.

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The chronic fatigue syndrome (CFS) is a disabling disease, mainly affecting adolescents and young adults.¹ The pathophysiology is unknown, but recent evidence suggests that abnormalities of cardiovascular regulation may play an important role in some cases. Various forms of orthostatic intolerance have been demonstrated both in adult^{2–4} and pediatric^{5–7} patients, as well as abnormalities in cerebral,⁸ muscle,⁹ and skin^{10,11} hemodynamics. Taken together, these observations indicate that CFS can be characterized by functional disturbances of the autonomic nervous system affecting cardiovascular regulation.^{12–14}

Analyses of heart rate variability during orthostatic stress provide information on cardiac autonomic control.^{15,16} However, CFS studies based on such methodology have yielded conflicting results,^{17–22} possibly related to the common use of an ordinary head-up tilt-test for the orthostatic challenge. In an experimental setting, the test may be inaccurate due to the varying effects of the muscle venous pump among different participants, and the high rate of false positives in adolescents.²³ In addition, in most prior studies the number of control subjects has been small, increasing the risk of type 2 errors.

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The technique of lower body negative pressure (LBNP) provides a more accurate tool for studies of cardiovascular adjustments during orthostatic stress.²⁴ To our knowledge, this method has not been previously used in a CFS study. Thus, the aim of this study was to explore heart rate variability at rest and during orthostatic challenge in adolescents with CFS, using LBNP and including a high number of control subjects. It was hypothesized that variability indices would differ between CFS patients and controls, both at rest and during orthostatic stress.

METHODS

Subjects

CFS patients aged 12–18 years were consecutively recruited from the outpatient clinic at the Department of Pediatrics, Rikshospitalet-Radiumhospitalet Medical Centre, serving as a national referral center for children and adolescents with 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). The main criterion of at least 6 months of chronic or relapsing fatigue, severely affecting daily activities²⁵ was required in this study. However, the CDC-definition also requires patients having at least 4 of 8 specific accompanying symptoms. Since the validity of this last demand has been questioned,²⁶ particularly in the pediatric population,²⁷ accompanying symptoms were not required in this study.

Healthy controls aged 12–18 years volunteered from local schools. In order to increase the statistical power, a 1:4 relation between patients and controls was sought. Through communication with the responsible teachers, a recruitment process was established that assured an equal distribution of age and sex between the two groups. Subjects having a chronic disease (such as allergy) or using any medications on a regular basis (including contraceptive pills) 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. They were in-

structed to fast overnight the day prior to the experiments.

Written, informed consent was obtained from all participants and their parents. The study was approved by the Regional Committee for Ethics in Medical Research.

LBNP with Handgrip

Experiments started at 11 a.m. The participants had been offered a light, standardized meal (1 to 2 pieces of bread, 1 glass of juice) 2 hours 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 predefined negative pressure within milliseconds.²⁸ 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.

Five minutes were used for baseline registration of cardiovascular variables. Then, LBNP of –20 mmHg was applied. After 6 minutes of LBNP, the subjects were asked to perform left-sided handgrip for 1 minute with 30% of maximal voluntary contraction force. This procedure was repeated once after a 1-minute resting interval. One minute after the termination of the second handgrip, LBNP was turned off. The cardiovascular adjustments during combined LBNP and handgrip will be reported elsewhere.

In two subjects (one 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 procedure was performed twice with a 5-minute rest period between applications of LBNP. However, two additional recordings were excluded from the analyses due to low technical quality.

Instantaneous heart rate (HR) was obtained from the RR interval (RRI) of the ECG. In addition, blood pressure, as well as aortic, brachial artery, and acral skin blood flow were recorded continuously and noninvasively. These measurements are not reported in this article. All recorded signals, including the pressure in the LBNP chamber, were online transferred to a recording computer running a program for real-time data acquisition (developed by Morten Eriksen, Dept. of Physiology, University of Oslo, Norway).

Data Analysis

Beat-to-beat recordings of RRI were converted to 3 Hz time series. For each experimental run, segments of 120-second length were selected, respectively, prior to LBNP and during LBNP prior to the handgrip periods, and subjected to spectral analyses using an autoregressive algorithm. Spectral components were decomposed, and power densities were computed in the low-frequency (LF) band (0.04–0.15 Hz) and the high-frequency (HF) band (0.15–0.5 Hz), and are expressed both in absolute (LF_{abs} , HF_{abs}) and normalized units, where $LF_{norm} = LF_{abs} / (LF_{abs} + HF_{abs})$ and $HF_{norm} = HF_{abs} / (LF_{abs} + HF_{abs})$. In addition, time-domain indices of variability were computed from the same segments: SDNN (the standard deviation of all RR-intervals), pNN50 (the proportion of successive RRIs with a difference greater than 50 ms), and r-MSSD (the square root of the mean square differences of successive RRIs). For subjects with two experimental recordings, the arithmetical mean for each variable was computed from corresponding experimental epochs.

Statistical analyses were carried out using SPSS statistical software. Based upon inspection of plots, most variables were appraised not to follow a normal distribution. Thus, results are expressed as median with nonparametric 95% confidence intervals. The nonparametric Wilcoxon–Mann–Whitney’s test (2-sided) was used to explore differences between the two groups. Since the research questions did not concern within group differences, statistical tests for repeated measurements were not applied. A P-value of ≤ 0.05 was considered statistically significant. In order to reduce the methodological problem of multiple comparisons, statistical tests were only performed for the variables at rest and during LBNP.

RESULTS

A total of 14 CFS patient and 56 healthy controls were included in the study (Table 1). The two groups were comparable regarding sex, age, weight, and height. All were of Caucasian ethnicity, except one control.

Mean duration of fatigue among the patients was 31 months. Their functional impairments were severe; they were physically inactive, did not participate in leisure activities, and had a high level of school absenteeism. However, no one was permanently bedridden.

At rest, CFS patients had significantly lower RRI (higher HR) than controls (Table 2), but no indices of variability were significantly different between the two groups. During LBNP, HR increased more among CFS patients than controls, enhancing the differences in RRI already present at baseline. In addition, HF_{abs} , HF_{norm} , and r-MSSD were significantly lower in CFS patients than in controls, whereas LF_{norm} and LF/HF were significantly higher.

DISCUSSION

Interpretation of RRI Variability Indices

The primary finding of this study is that mild orthostatic stress in adolescents with CFS results in heart rate and heart rate variability responses that differ from normal controls, characterized by a greater decrease in RRI and HF-indices, and a greater increase in LF-indices and the LF/HF-ratio.

Spectral analyses of short-time recordings of RRI usually reveal three distinct peaks in the power spectrum.²⁹ By convention, spectral power densities are computed in three frequency bands corresponding to these peaks, assigned very low

Table 1. Subject Characteristics

	Control		Chronic Fatigue	
	n	%	n	%
Number	56		14	
Female gender	33	58.9	9	64.3
	Mean	(range)	Mean	(range)
Age (years)	15.6	(13–18)	15.2	(12–18)
Weight (kg)	61.6	(44–99)	59.5	(43–92)
Height (cm)	171.5	(149–195)	172.2	(160–192)
Body surface area (m ²)	1.7	(1.4–2.2)	1.7	(1.4–2.2)
Duration of fatigue (months)			31.3	(6–60)

Table 2. RRI and Indices of Heart Rate Variability at Rest and during LBNP 20 mmHg. Median (95 % Confidence Interval)*

	At Rest		During LBNP		Δ (Rest-LBNP)	
	Control	CFS	Control	CFS	Control	CFS
RRI	921 (887–968)	834 [†] (736–908)	847 (793–887)	696 [‡] (645–744)	–81 (–99 to –75)	–113 (–166 to –74)
Total power (ms ²)	3526 (2424–4551)	2633 (1162–4932)	3477 (2041–4004)	2450 (984–3889)	–255 (–659–284)	–740 (–1952–835)
LF _{abs} (ms ²)	833 (567–1260)	673 (450–1694)	941 (798–1094)	766 (552–1063)	75 (–144–346)	–4.6 (–313–538)
HF _{abs} (ms ²)	1011 (531–1866)	592 (336–2195)	447 (325–808)	270 [†] (123–447)	–279 (–567 to –137)	–275 (–1842 to –41)
LF _{norm} (nu)	41.5 (34.8–47.5)	44.0 (39.7–53.0)	57.4 (52.8–66.1)	72.8 [†] (58.2–82.8)	15.7 (9.8–20.6)	32.7 (13.1–37.9)
HF _{norm} (nu)	57.5 (51.7–63.7)	54.1 (45.3–56.8)	41.8 (32.7–46.2)	26.2 [†] (16.6–41.0)	–15.4 (–21.2 to –9.0)	–31.6 (–37.0 to –4.8)
LF/HF	0.83 (0.56–1.13)	0.93 (0.70–1.70)	1.92 (1.34–2.47)	2.99 [†] (1.46–6.75)	0.88 (0.41–1.79)	1.90 (0.15–4.77)
SDNN (ms)	55.5 (48.6–66.1)	51.3 (33.4–72.6)	57.3 (45.2–62.3)	47.7 (30.7–63.4)	–2.7 (–6.1–1.8)	–11.6 (–20.6–8.3)
pNN50 (%)	14.1 (7.7–21.5)	8.9 (2.3–22.4)	5.8 (2.8–9.7)	2.3 (0.88–8.1)	–5.1 (–7.5 to –2.9)	–2.9 (–17.2 to –0.1)
r-MSSD (ms)	49.7 (40.3–65.1)	38.8 (22.7–80.6)	32.7 (26.1–41.1)	23.2 [†] (17.5–35.2)	–15.2 (–19.9 to –7.8)	–11.4 (–50.0 to –2.2)

*In order to reduce the problem of multiple comparisons, statistical tests were only performed for variables at rest and during LBNP.

[†]P ≤ 0.05 compared with controls, Wilcoxon-Mann-Whitney's test.

[‡]P ≤ 0.001 compared with controls, Wilcoxon-Mann-Whitney's test.

RRI = RR interval; LF abs = variability in the LF region, absolute values; HF abs = variability in the HF region, absolute values; LF norm = variability in the LF region, normalized values; HF norm = variability in the HF region, normalized values; LF/HF = LFabs divided by HFabs; SDNN = standard deviation of all RR-intervals; pNN50 = the proportion of successive RRs with a difference greater than 50 ms; r-MSSD = the square root of the mean square differences of successive RRs; nu = normalized units.

frequency (VLF, ≤ 0.04 Hz), low frequency (LF, 0.04–0.15 Hz), and high frequency (HF, 0.15–0.5 Hz), respectively. Variability of RRI in the HF region is directly related to respiratory activity.¹⁶ Although the exact origin of this rhythm remains an area of controversy, it is mediated by variations of efferent vagal (parasympathetic) neural activity,^{15,16} and RRI power spectral density in the HF-band is an index of vagal modulation of heart rate. Variability of RRI in the LF region is due to the combined effect of cardiac vagal and sympathetic activity in response to a variety of inputs including blood pressure, temperature, and low-frequency respiratory activity.^{15,16,30} The LF/HF-ratio of RRI has often been regarded as a measure of "sympathovagal balance" in the modulation of HR, particularly during orthostatic stress.^{31,32}

In this study, the group differences in LF/HF, HF_{norm}, and LF_{norm} upon orthostatic stress can be attributed primarily to a significant decrease in

HF_{abs} among the CFS patients. This notion is, in addition, supported by the concomitant reduction of r-MSSD in the patient group, as this variable is typically correlated with HF power for RRI.²⁹ The underlying mechanism is probably a reduction in vagal modulation of heart rate, but increased sympathetic modulation of heart rate might also contribute. In any case, it can be concluded that adolescent CFS patients, as compared to controls, appear to have enhanced vagal withdrawal and therefore a sympathetic predominance in heart rate control upon mild orthostatic stress, explaining the greater HR increase observed in the patient group.

These results correspond neatly to findings obtained during low-grade (20°) head-up tilting of a larger group of adolescent CFS patients in our laboratory.^{7,33} As compared to LBNP, tilt-test constitutes a different experimental situation because the muscle venous pump and vestibular reflexes

are activated. Still, the hemodynamic responses among CFS patients closely resembled those reported here, indicating enhanced sympathetic cardiovascular control.

Also, in a study of adolescent CFS patients, Stewart reported similar results during 60° head-up tilt-test, and also found evidence of sympathetic predominance at supine rest.²² However, findings in adult CFS patients have varied from no abnormalities,^{17,20} to increased LF variability,¹⁹ and increased instant center frequency (an index of sympathovagal balance).¹⁸ Differences from this study might be explained by different inclusion criteria, experimental protocols, and mathematical algorithms for the spectral analyses. In addition, most previous reports are weakened by relatively small control groups, thus increasing the risk of type 2 errors. Interestingly, Yataco and colleagues¹⁷ did identify differences between CFS patients and controls similar to those reported in this article; however, their study included only 11 controls, and the differences did not reach statistical significance.

Cardiovascular Dysregulation in CFS

In agreement with past reports, the data from this report suggest that some CFS patients suffer from functional disturbances of the autonomic nervous system affecting cardiovascular regulation. Absolute or relative hypovolemia at baseline, which has been found in some studies of CFS patients,^{34–36} is a possible underlying mechanism. Interestingly, the findings reported by Streeten and co-workers indicate that the underlying mechanism might be subnormal erythrocyte volume, and that the hemodynamic abnormalities could be reversed by application of antishock trousers.³⁶ Hypovolemia is characterized by a general enhancement of sympathetic cardiovascular activity during orthostatic stress, causing changes in cardiovascular variability similar to our findings.^{37–39}

An alternative explanation is an abnormality of 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,⁴ and similar results have been reported in adolescents.²²

A third possibility is cardiovascular deconditioning.⁴⁰ Physical inactivity is associated with higher

resting HR,⁴¹ which might increase even further during periods of bed rest.⁴² However, both sedentary and gravitational deconditioning seem to be associated with attenuated sympathetic responsiveness during orthostatic stress.^{42,43} The amount of gravitational stimuli necessary to prevent deconditioning remains a question of debate. Most studies addressing this topic have exposed the subjects to a very strict bed-rest regimen lasting weeks or months. Moreover, evidence from both human and animal studies suggests that intermittent exposure to gravity during a bed-rest period is sufficient to prevent gravitational deconditioning.^{44,45} Since none of the CFS patients in this study were permanently bedridden, it seems unlikely that deconditioning alone can explain the results.

Study Limitations

Blood and/or plasma volume were not measured, leaving the question of hypovolemia unresolved. Further data analyses involving computation of baroreceptor gain could have shed light on possible abnormalities of the baroreflex mechanism. Finally, respiratory activity has been shown to change during orthostatic challenge, and could therefore influence cardiovascular variability;⁴⁶ however, ventilation was not controlled for in this study.

CONCLUSIONS

The results of this study demonstrate that adolescents with CFS appear to have enhanced vagal withdrawal and therefore a sympathetic predominance of heart rate control during mild orthostatic stress. Future research should specifically address the possibilities that moderate hypovolemia and abnormalities in reflex mechanisms are underlying mechanisms.

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