Usefulness of an Abnormal Cardiovascular Response During Low-Grade Head-Up Tilt-Test for Discriminating Adolescents With Chronic Fatigue from Healthy Controls

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Hemodynamic dysfunction is documented in chronic fatigue syndrome (CFS). This study was conducted to investigate cardiovascular responses to orthostatic stress in adolescents with CFS, using a novel procedure for tilt-table testing. A total of 27 adolescents with CFS and 33 healthy control subjects with equal age and gender distribution underwent 15 minutes of 20° head-up tilt testing. Heart rate, systolic blood pressure (BP), mean BP, diastolic BP, stroke index, total peripheral resistance index, end-diastolic volume index, and acceleration index were continuously and noninvasively recorded. At rest, patients with CFS had higher total peripheral resistance index values ($p < 0.01$) and lower stroke index and end-diastolic volume index values ($p < 0.05$) than controls. During 20° head-up tilt testing, patients with CFS had greater increases in heart rate, diastolic BP ($p < 0.001$), mean BP ($p < 0.01$), and total peripheral resistance index ($p < 0.05$) than controls and greater decreases in stroke index ($p < 0.05$). Syncope or near syncope was not observed. In conclusion, this study found that adolescents with CFS have significant abnormalities of cardiovascular regulation in response to mild orthostatic stress, differentiating them from healthy controls. **© 2007 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2007;99: 997–1001)**

Chronic fatigue syndrome (CFS) is related to abnormalities of orthostatic cardiovascular regulation in adult[1–3] as well as pediatric[4,5] patients. The head-up tilt test (HUT) is therefore a potentially useful diagnostic procedure. However, the tolerance for orthostatic stress is lower in adolescents than in children and adults, and conventional procedures of the HUT are burdened by a high rate of false-positive results in this age group, making the test less informative.[6] We hypothesized that a novel, low-grade HUT would be useful in discriminating patients with CFS from healthy controls.

Methods

Subjects: Patients with CFS ranging from 13 to 18 years of age were consecutively recruited from the pediatric outpatient clinic at 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, in which the main criterion is ≥6 months of chronic or relapsing fatigue, severely affecting daily activities.[7] In addition, according to this definition, patients should report ≥4 of 8 specific accompanying symptoms (headache, muscle pain, joint pain, sore throat, tender lymph nodes, impaired memory or concentration, unrefreshing sleep, and malaise after exertion). However, the validity of this definition has been criticized in adults[8,9] and children.[10] Participation in this study required only 4 months of chronic or relapsing fatigue and no accompanying symptoms.

Healthy controls aged 13 to 18 years with similar distributions of gender and age volunteered from local schools. Subjects with chronic diseases (such as allergies) or using drugs (including contraceptive pills) on a regular basis were excluded.

One week before 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 requested to fast 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,[11] were translated into Norwegian by 1 of the investigators (VBW) and slightly modified to fit our particular age group. On the basis of personal clinical experience with patients with CFS, we added

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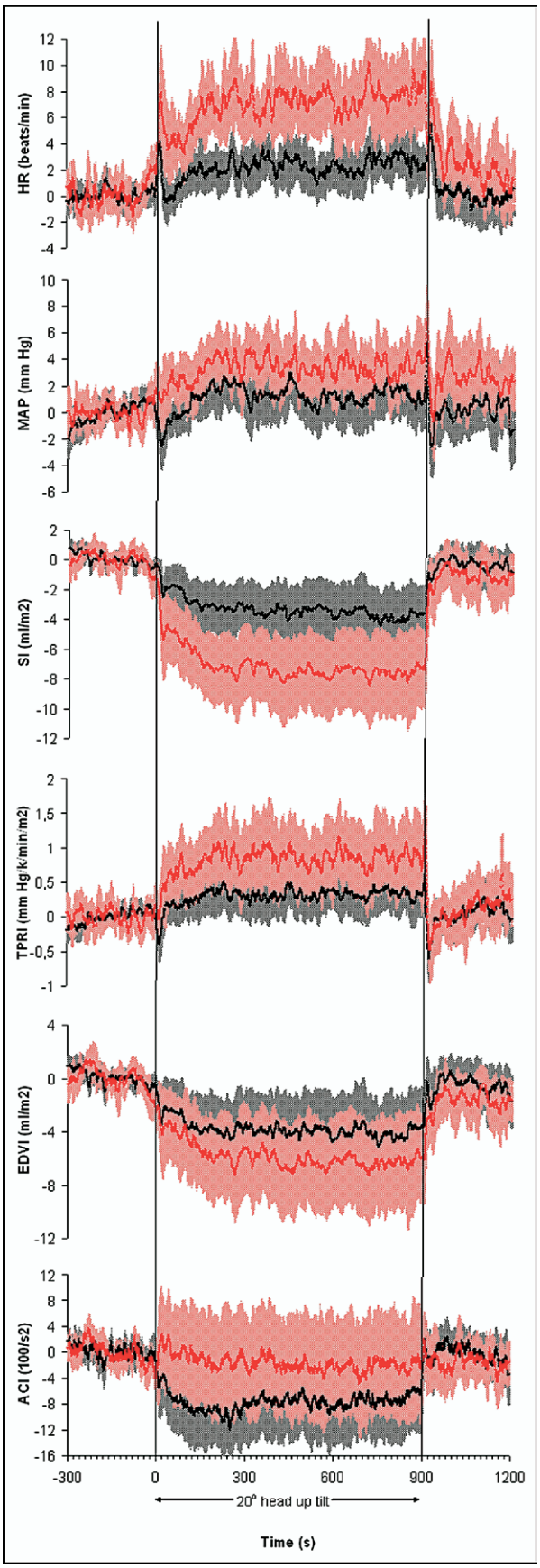

questions focusing on the functional consequences of this disease. The subjects answered by interview.

HUT: The experimental part of this study was undertaken in the Department of Pediatrics at Rikshospitalet-Radiumhospitalet Medical Centre. All experiments started at 9 A.M. and were carried out in a quiet room with dimmed lights and no windows.[12] The ambient temperature was kept at about 23°C. The participants had been offered a light meal (1 or 2 pieces of bread, 1 glass of juice) 30 minutes before testing but were otherwise not allowed to eat or drink. They were lightly dressed.

The subjects lay supine on an electronically operated tilt table with foot-board support (model 900-00, CNSystems Medizintechnik, Graz, Austria). They were attached to the Task Force Monitor (model 3040i, CNSystems Medizintechnik), a combined hardware and software device for the noninvasive recording of cardiovascular variables.[13]

Five-minute baseline recordings were obtained. Subjects were then head-up tilted 20° over approximately 10 seconds. They were maintained at 20° for 15 minutes and then tilted back to the horizontal position, after which the recordings were continued for another 5 minutes, making the total experimental period 25 minutes (Figure 1). Subjects were asked not to speak during the recording period.

Instantaneous heart rate (HR) was obtained from the RR interval of the electrocardiogram. Photoplethysmography on the right middle finger was used to obtain a noninvasive, continuous recording of arterial blood pressure (BP). This method correlates satisfactorily with invasive pressure measurements[14] and has also been validated in adolescents and children.[15] Approximately every minute, the recorded values were calibrated against conventional oscillometric measurements of arterial BP on the subjects' left arms. The method of impedance cardiography, in which a small electrical potential is applied between electrodes placed on the neck and upper abdomen, was used to obtain a continuous recording of the temporal derivative of the transthoracic impedance (dZ/dt).[16]

All recorded signals were transferred on-line to the built-in recording computer of the Task Force Monitor, running software for real-time data acquisition. Beat-to-beat mean arterial BP was calculated by numerical integration of the recorded instantaneous BP. Beat-to-beat stroke volume and end-diastolic volume of the left ventricle were calculated from the impedance signal.[13,17] This method has been validated in adults[18] and children.[19] The highest positive slope of the impedance signal (d^2Z/dt^2_{max}) corresponds to the maximal acceleration of blood flow during the ejection phase and is thus partly dependent on the inotropic state of the myocardium.[20]

Figure 1. Mean changes in cardiovascular variables (based on coherent averaging of individual recordings) in controls *(black)* and patients with CFS *(red)* during a 20° HUT. *Shaded areas,* 95% confidence intervals for the mean (shown for clarity, although the consecutive data points are not independent of one another). Data are normalized to zero for the first time period. The time axis is adjusted so that zero corresponds to the start of tilting. ACI = acceleration index; MBP = mean BP; SI = stroke index.

Table 1
Cardiovascular variables during 20° head-up tilt test*

Variable	Baseline		Early Tilt		Δ Tilt		Late Tilt		After Tilt	
	Controls	Subjects with CFS	Controls	Subjects with CFS	Controls	Subjects with CFS	Controls	Subjects with CFS	Controls	Subjects with CFS
HR (beats/min)	67 (63 to 70)	70 (65 to 75)	68 (64 to 71)	75 (69 to 80)	1.0 (−0.4 to 2.3)	4.5§ (2.8 to 6.2)	70 (65 to 74)	78 (72 to 84)	67 (63 to 71)	73 (68 to 78)
Systolic BP (mm Hg)	112 (109 to 115)	109 (105 to 112)	111 (107 to 114)	109 (106 to 113)	−1.3 (−2.8 to 0.3)	0.8† (−0.7 to 1.9)	111 (107 to 115)	110 (107 to 114)	111 (107 to 116)	110 (106 to 115)
Mean BP (mm Hg)	80 (78 to 82)	79 (76 to 82)	80 (77 to 82)	82 (78 to 85)	−0.2 (−1.3 to 1.0)	2.5‡ (0.9 to 4.0)	81 (78 to 84)	82 (80 to 86)	80 (77 to 83)	82 (79 to 86)
Diastolic BP (mm Hg)	65 (63 to 67)	65 (62 to 68)	65 (63 to 68)	68 (64 to 71)	−0.01 (−1.1 to 1.1)	2.9§ (1.4 to 4.5)	67 (64 to 70)	69 (66 to 71)	65 (62 to 68)	68 (65 to 71)
Stroke index (ml/m^2)	58 (55 to 60)	52† (49 to 56)	55 (53 to 58)	47 (44 to 50)	−2.3 (−3.8 to −0.8)	−5.7† (−7.9 to −3.6)	54 (51 to 56)	45 (42 to 47)	58 (55 to 60)	51 (48 to 54)
TPRI (mm Hg/L/min/m^2)	7.5 (7.0 to 8.0)	8.8‡ (7.9 to 9.7)	7.6 (7.2 to 8.1)	9.5 (8.5 to 11)	0.1 (−0.08 to 0.4)	0.7† (0.3 to 1.1)	7.8 (7.4 to 8.2)	9.9 (8.9 to 11)	7.4 (6.9 to 7.9)	8.8 (8.0 to 9.7)
EDVI (ml/m^2)	89 (85 to 93)	82† (77 to 87)	86 (83 to 89)	78 (74 to 82)	−3.0 (−5.4 to −0.6)	−3.9 (−5.9 to −0.7)	85 (82 to 87)	76 (72 to 79)	89 (85 to 93)	80 (76 to 85)
Acceleration index ($100/s^2$)	86 (78 to 94)	79 (69 to 88)	79 (72 to 85)	80 (70 to 90)	−7.3 (−12 to −2.2)	1.0 (−6.0 to 8.0)	79 (73 to 85)	79 (69 to 88)	86 (78 to 95)	77 (68 to 87)

Data are expressed as mean (95% confidence interval).

* Because of technical problems, the impedance signal was not obtained from 1 patient with CFS. To reduce the methodologic problem of multiple comparisons, statistical tests were performed only for the cardiovascular variables baseline and Δ tilt.

† $p \leq 0.05$ for differences between groups, Wilcoxon-Mann-Whitney test.

‡ $p \leq 0.01$ for differences between groups, Wilcoxon-Mann-Whitney test.

§ $p \leq 0.001$ for differences between groups, Wilcoxon-Mann-Whitney test.

Table 2
Subject characteristics

Variable	Controls (n = 33)	Subjects With CFS (n = 27)
Women	19 (58%)	18 (68%)
	Mean (range)	Mean (range)
Age (yrs)	15 (13–18)	15 (13–18)
Weight (kg)	61 (44–77)	56 (37–92)
Height (cm)	172 (149–195)	169 (145–197)
Body surface area (m^2)	1.7 (1.4–2.0)	1.6 (1.3–2.3)
Reported physical exercise (h/wk)	6.7 (2–14)	0.5 (0–6)
Duration of fatigue (mo)		30 (4–132)
School absence ≥1/wk	0	23 (85%)
Absence from leisure activities ≥1/wk	0	24 (96%)
Permanently bedridden	0	0

Data were exported to Microsoft Excel (Microsoft Corporation, Redmond, Washington) for further calculations. Beat-to-beat stroke index and end-diastolic volume index (EDVI) were obtained by dividing stroke volume and end-diastolic volume by body surface area, estimated from the subjects' height and weight. Beat-to-beat total peripheral resistance index (TPRI) was calculated as mean BP divided by the product of stroke index and HR.

Data analysis: For each experimental run of the HUT, the median of all cardiovascular variables was computed in the following time periods: 150 to 270 seconds (baseline), 330 to 450 seconds (early tilt), 1,050 to 1,170 seconds (late tilt), and 1,230 to 1,350 seconds (after tilt). Delta tilt (early tilt − baseline) was also computed. We then computed the means of these data for the 2 groups.

To visualize the changes in cardiovascular variables during the HUT in the 2 groups (Figure 1), the recordings from each subject were converted to a 4-Hz time series of equal length by linear interpolation. The time series were filtered by assigning the median value within a 10-second sliding window to each time point, thus removing minor artifacts and normal high-frequency variability.[21] 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.[22]

The statistical analyses were carried out using SPSS statistical software (SPSS Inc., Chicago, Illinois). On the basis of the inspection of plots, all variables were appraised to follow an approximately normal distribution, and results are therefore expressed as means with 95% confidence intervals (Table 1). However, because of the presence of occasional outliers, we used the nonparametric Wilcoxon-Mann-Whitney test (2 sided) to explore differences between the 2 groups. A p value ≤0.05 was considered statistically significant. To reduce the methodologic problem of multiple comparisons, statistical tests were performed only for the cardiovascular variables of baseline and Δtilt (Table 1). Among these variables, the changes in HR, mean BP, TPRI, and stroke index during tilt were considered most central to our research aim.

Results

A total of 27 patients with CFS and 33 healthy controls were included in the study (Table 2). All were of Caucasian ethnicity. The patients with CFS were physically inactive, did not participate in leisure activities, and had high levels of school absence. However, none was permanently bedridden.

At rest, the patients with CFS had significantly higher TPRI values and significantly lower stroke index and EDVI values than controls (Table 1). HRs were also higher and acceleration index values lower in the patients with CFS, but the differences were not statistically significant. During tilt, the patients with CFS had greater increases in HR, mean BP, diastolic BP, and TPRI and greater decreases in stroke index than controls (Table 1 and Figure 1). EDVI decreased similarly in the 2 groups. Acceleration index decreased in controls but tended to increase in CFS patients. After tilting, all variables in the 2 groups returned to levels similar to those observed at baseline.

Syncope or near syncope during tilting was not observed in either of the 2 groups. In 1 patient with CFS, the test was terminated earlier than scheduled because of subjective complaints of dizziness; however, no significant changes in hemodynamic variables were recorded.

Discussion

The most important findings in this study are that (1) at rest, patients with CFS have higher HRs, higher TPRI values, lower stroke index values, and lower EDVI values than controls; and (2) during orthostatic stress, patients with CFS have larger increases in HR, mean BP, diastolic BP, and TPRI, no decreases in acceleration index, and larger decreases in stroke index than controls. These deviations were strikingly homogenous within the patient group and significantly different from controls, despite the small number of subjects studied and the application of very mild orthostatic stress. Thus, a low-grade HUT combined with noninvasive measurements of multiple cardiovascular variables is an informative procedure.

To our knowledge, the findings at supine rest have not been reported in adolescents. However, some studies of adult patients with CFS have provided slight evidence of similar disturbances in baseline hemodynamics.[3,23,24] There are a variety of possible explanations. Moderate hypovolemia, which indeed has been found in 1 study of CFS,[25] can explain all the findings. An alternative explanation is a general enhancement of sympathetic efferent activity due either to changes in peripheral autonomic neuronal control or to changes in the brainstem cardiovascular control center. If so, the reduced EDVI and stroke index must be attributed to increased HR and reduced diastolic filling time.[26]

The findings during the HUT appear to indicate an enhanced sympathetic response to orthostatic stress in the patients with CFS. A reduction in acceleration index, as observed in controls, is expected because of reduced cardiac filling and thereby reduced ventricular performance according to the Frank-Starling mechanism. A tendency toward increased acceleration index, as observed in patients with CFS, therefore points to an increased cardiac inotropic effect, further indicating a general enhancement of cardiovas-

cular sympathetic efferent activity. Moderate hypovolemia and cardiovascular deconditioning are possible explanations for these findings as well.[27,28]

Similar HR responses during orthostatic stress have been observed by others in adult and pediatric populations.[1–5,29] The reports of BP responses are more conflicting. For instance, Freeman and Komaroff[29] found a larger decrease in diastolic BP in patients with CFS during a 60° HUT, whereas we observed an increase. Likewise, Stewart et al[5] reported a decrease in systolic BP in adolescent patients with CFS during the HUT, whereas our patients did not differ from controls. However, these apparent contradictions may be explained by the different test procedures. In general, our results suggest that CFS patients have more comprehensive disturbances of cardiovascular regulation than previously acknowledged.

Plasma catecholamines were not measured during the HUT but could have strengthened our hypothesis of enhanced sympathetic response to mild orthostatic stress. Nor did we measure blood volume and plasma volume at baseline, leaving the question of hypovolemia in patients with CFS unresolved. Allowing the subjects to eat before the HUT could have decreased their orthostatic tolerance. Finally, although the validity of impedance cardiography has been thoroughly documented, there are also studies questioning its usefulness.[30] The evidence supporting the validity of indexes derived from the impedance signal, such as EDVI and acceleration index, is generally weaker.

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