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Autonomic function in patients with chronic fatigue syndrome

P.M.M.B. Soetekouw, M.D.,[1] J.W.M. Lenders, M.D., Ph.D.,[1] G. Bleijenberg, Ph.D.,[2] Th. Thien, M.D., Ph.D.,[1] and J.W.M. van der Meer, M.D., Ph.D.[1]

[1]Department of Medicine, Division of General Internal Medicine and [2]Department of Medical Psychology, St. Radboud University Hospital, Nijmegen, The Netherlands

Address correspondence and reprint requests to Dr. P.M.M.B. Soetekouw, Department of Medicine, Division of General Internal Medicine 541, St. Radboud University Hospital, P.O. Box 9101, 6500 HB, Nijmegen, The Netherlands

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Subtle signs of autonomic dysfunction and orthostatic intolerance have been reported in patients with chronic fatigue syndrome (CFS). To assess cardiovascular autonomic function noninvasively in an unselected group of patients with CFS, we examined responsiveness to several cardiovascular reflex tests in 37 CFS patients and 38 healthy control subjects. Blood pressure and heart rate (HR) were recorded continuously by a Finapres device before and during forced breathing, standing up, Valsalva maneuver, and sustained handgrip exercise (HG). In addition, a mental arithmetic test was carried out and questionnaires to assess the severity of CFS symptoms were completed. At rest, there were no significant differences in blood pressure or in HR between the two groups. The in- and expiratory difference in HR tended to be lower in CFS patients (28.4 ± 10.5 beats) than in healthy controls (32.2 ± 9.5) ($p = 0.11$). The maximal increase in HR during standing up was not significantly different between the CFS group (37.6 ± 8.9 beats) and the control group (40.2 ± 8.9 beats). There were no significant differences between both groups with regard to the Valsalva ratio, but the systolic and diastolic blood pressure responses were significantly larger in CFS patients, despite the fact that many CFS patients were not able to sustain the Valsalva maneuver. The HR response to MA was significantly less in the CFS group (22.6 ± 9.9) than in the control group (29.5 ± 16.7) ($p < 0.05$), suggesting impaired cardiac sympathetic responsiveness to mental stress. The lower HR responses could not be explained by the level of concentration in the CFS group. During HG exercise, the hemodynamic responses were lower in the CFS group than in the control group, but this might be attributed to the lower level of muscle exertion in CFS patients. There were no significant differences between CFS patients with and without symptoms of autonomic dysfunction regarding the hemodynamic responses to the cardiovascular reflex tests. The findings of the study suggest that there are no gross alterations in cardiovascular autonomic function in patients with CFS.

Key words: chronic fatigue syndrome, autonomic nervous system

Chronic fatigue syndrome (CFS) is a medically unexplained syndrome consisting of chronic fatigue for a period of at least 6 months and a severely impaired daily activity level [1]. The fatigue is often accompanied by a variety of nonspecific symptoms and signs like low-grade fever, arthralgias, myalgias, postexertional fatigue, neuropsychological complaints, and sleep disorders [1,2]. The etiology is still unknown although numerous somatic and psychological hypotheses have been postulated [3,4]. Some CFS patients complain of increased perspiration, urinary frequency, nocturia, palpitations, and diarrhea, suggesting dysfunction of the autonomic nervous system. On the other hand, specific autonomic disorders like pure autonomic failure or multiple system atrophy can also give rise to fatigue [5]. In addition, some studies have found abnormal cardiovascular responses to head-up tilt testing, also suggesting that abnormal autonomic responses occur at least in some CFS patients [6–12]. The objective of the authors' study was to examine whether patients with CFS, who were not selected for having complaints fitting with autonomic dysfunction, have altered responses to several autonomic function tests. All subjects underwent five accepted noninvasive cardiovascular reflex tests [13,14] and a mental arithmetic test. They also underwent a psychological assessment to determine some dimensions of fatigue and level of functional impairment and to investigate if there is a relation between these levels of complaints and the hemodynamic responses to the reflex tests.

Methods

Subjects

From a database of CFS patients, originally referred to the Department of General Internal Medicine of the St. Radboud University Hospital Nijmegen, a group of 54 patients were selected. In these patients the diagnosis of CFS was made according to the inclusion and exclusion criteria of Sharpe *et al.* [15]. Patients had to have fatigue with substantial impairment in their daily life, which means a score of 35 or more on the subjective fatigue subscale of the Checklist Individual Strength [2] and a score of 750 or more on the weighted total score of the Sickness Impact Profile [16,17]. The additional

exclusion criteria for this study were drug treatment for hypertension, chronic obstructive pulmonary disease (COPD), and using antidepressant drugs. Seventeen patients who were selected for this study had to be excluded for different reasons, *e.g.*, too large travel distance to the hospital. Finally, 37 patients and 38 control subjects were enrolled.

The participating CFS patients, 30 women and 7 men, had a mean age of 33.6 (± 7.7) years. The CFS diagnosis was made 0 to 5 years ago. The control group consisted of 38 healthy volunteers, 28 women and 10 men (32.5 ± 7.2 years), matched for age and gender who had a nonmedical background. Twenty-two of them had already participated in previous research protocols of a different nature. None of the healthy subjects suffered from cardiovascular disease, COPD, diabetes mellitus, or central nervous system disease. The controls did not use any medication. The study protocol was approved by the ethics committee of the St. Radboud University Hospital Nijmegen and all subjects gave informed consent.

Study protocol

Patients and control subjects were examined in a quiet room with a constant temperature (22.9 ± 0.7°C) and humidity (53.3 ± 9.9%). All subjects were asked to refrain from caffeine, alcohol, and tobacco for at least 12 hours before the study and not to eat or drink 4 hours before the tests. All subjects had to complete three questionnaires. The Checklist Individual Strength (CIS) is a reliable and validated questionnaire that measures four aspects of fatigue, namely subjective level of fatigue, concentration, motivation, and physical activity [2]. High scores indicate a high level of fatigue, a high level of concentration problems, low motivation, and a low level of physical activity. The Sickness Impact Profile (SIP) measures the influence of symptoms on daily functioning [16,17], using the following eight subscales: home management, mobility, alertness behavior, sleep/rest, ambulation, social interactions, work and recreation, and pastimes. The Symptom Checklist-90 (SCL-90) is an indicator of psychopathology and screens for anxiety, agoraphobia, depression, somatization, cognitive difficulties, interpersonal sensitivity, hostility, and sleep disturbances [18]. In addition, all subjects were questioned whether they had complaints suggesting autonomic dysfunction and how many hours they were in bed at night and during the day. After completing all questionnaires, systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were measured three times in the supine position after 5 minutes of rest. The average value of these three measurements was taken as the baseline supine blood pressure and heart rate. After 1 minute of standing, blood pressure and heart rate were measured again. Orthostatic hypotension was defined as a decrease in systolic blood pressure of 20 mm Hg or more after 1 minute of standing. After these measurements the cardiovascular reflex tests were explained and tried out in order to make all subjects familiar with these procedures.

All subjects underwent six tests: forced breathing, standing up, Valsalva maneuver, mental arithmetic test, and sustained handgrip exercise [19]. Before and during these tests, blood pressure and heart rate were recorded continuously by a Finapres device (Ohmeda, USA). The Finapres cuff was wrapped around the middle finger of the nondominant arm and was precisely fixed at heart level. During the forced breathing test the subjects performed maximal respirations in the supine position at a rate of six breaths per minute after 5 minutes of supine rest. The heart rate difference between in- and expiration was calculated and averaged for six cycles (I-E difference). Standing up was started after 5 minutes of supine rest. The maneuver was performed in 2 to 3 seconds and the subjects remained standing for 2 minutes. Standing blood pressure was calculated as the average over the time period between 50 and 80 seconds. The blood pressure response to standing was calculated as the difference between the maximum standing blood pressure and the baseline blood pressure recorded during 1 minute before standing. The delta HR max (delta: difference; max: maximal) was defined as the difference between the maximum heart rate after standing and baseline heart rate. The t/b (tachycardia/bradycardia) ratio was calculated as the quotient of maximum heart rate and minimum heart rate after standing up. The Valsalva maneuver was performed three times in the sitting position, each after at least 1 minute of rest. The subjects were instructed to maintain an expiratory pressure of 40 mm Hg over 15 seconds by means of forced expiration into a mouthpiece connected to a sphygmomanometer. Closure of the glottis was prevented by a small leak to maintain a flow of air. The Valsalva ratio was defined as the maximum heart rate during the maneuver divided by the minimum heart rate after the maneuver. The three lowest blood pressure values and the three last blood pressure values during phase II were averaged. The differences between baseline blood pressure values before the Valsalva maneuver and the overshoot of blood pressure immediately after stopping expiration were averaged. After the Valsalva maneuver the subjects rested in a sitting position for 10 minutes, of which the last 5 minutes were recorded as the baseline period for the mental arithmetic test. During this test the subjects were repeatedly urged to subtract the two-digit number 17 from a large four-digit number until zero. At the beginning of this cognitive stress task a metronome was set at 60 beats per minute being increased to 208 beats per minute in four steps. The number of subtractions and the number of mistakes were recorded. Blood pressure and heart rate values were averaged over each 5-second periods for 5 minutes. The differences between maximum values of blood pressure and heart rate and baseline values of blood pressure and heart rate were calculated as the responses to the mental arithmetic test. A sustained handgrip exercise test was performed in the sitting position by squeezing a calibrated dynamometer at 30% of maximal voluntary contraction. The strength of contraction was also recorded. The maximal responses of blood pressure and heart rate during handgrip exercise were calculated.

Data analysis

Results are given as mean ± SD unless indicated otherwise. Statistical analysis was performed using SPSS (Statistical

Table 1. Complaints possibly related to autonomic dysfunction in patients with chronic fatigue syndrome (CFS) and in a healthy control group (controls)

	CFS (n = 37)	Controls (n = 38)	p value*
Perspiration increased	21 (57%)	5 (13%)	$p < 0.001$
Salivation decreased	9 (24%)	1 (3%)	$p < 0.05$
Dysphagia/pyrosis	9 (24%)	0 (0%)	$p < 0.05$
Constipation	8 (22%)	1 (3%)	$p < 0.05$
Weight increase	6 (16%)	3 (8%)	NS
Loss of weight	5 (14%)	2 (5%)	NS
Perspiration decreased	2 (5%)	0 (0%)	NS
Diuresis complaints	1 (3%)	0 (0%)	NS
Salivation increased	0 (0%)	1 (3%)	NS
Diarrhoea at night	0 (0%)	0 (0%)	NS
Impotence	0 (0%)	0 (0%)	NS

*p values are for the Fischer's exact test.

Package for the Social Sciences) for Windows 6.1.3 (SPSS Inc., Chicago, IL). Differences between patients and controls with regard to the hemodynamic parameters were tested using the unpaired Student's *t*-test. The Mann-Whitney rank-sum test was used for the scores of the questionnaires and the hours spent in bed during night and daytime. Fisher's exact test was used for the autonomic dysfunction complaints. The Spearman rank correlation coefficient was used for analyzing possible relevant relations between the responses to some of the psychological questionnaires and the autonomic reflex tests. When a correlation was found, then the hemodynamic parameters were again assessed by ANCOVA for correction for covariates. A two-sided $p < 0.05$ was taken as the level of significance.

Results

Baseline values

Table 1 demonstrates that 57% of the CFS patients complained of increased sweating as compared to 13% of the healthy controls ($p < 0.001$) and nearly 25% had decreased salivation, dysphagia, pyrosis, or constipation as compared to none of the controls ($p < 0.05$). The scores of the three psychological questionnaires are shown in Table 2. As expected, patients with CFS scored significantly higher for each factor as compared to the control group. They were more fatigued, had more concentration problems, were less motivated, showed less physical activity, had higher depression scores, and experienced more functional impairment. The CFS patients stayed 10 (median); 9 to 12 (interquartile range) hours in bed during the night and this was significantly longer than for the controls (8; 7–9 hours)($p < 0.001$). During the day, CFS patients were in bed during 2; 1 to 3 hours while this was 0; 0 to 0 hours in the controls ($p < 0.001$).

At supine rest there were no differences in supine blood pressure (CFS: 114.5 ± 7.6/71.8 ± 7.4; controls: 116.3 ± 9.5/72.9 ± 7.0 mm Hg) or heart rate (CFS: 69.2 ± 15.0; controls: 64.4 ± 12.6 beats/min) between the two groups. The standing blood pressure values were also not different between both groups. No CFS subjects had orthostatic hypotension defined as a decrease in systolic blood pressure of more than 20 mm Hg after 1 minute of standing.

Reflex tests

The hemodynamic responses to the 5 cardiovascular reflex tests are shown in Table 3. The I-E difference during forced breathing and the delta HR max during standing up tended to be lower in CFS patients than in the healthy controls but these differences did not reach statistical significance (forced breathing: $p = 0.11$; standing up: $p = 0.21$). The lowest SBP during phase II was similar between both groups. The lowest DBP during phase II was significantly higher in CFS patients than in controls. The means of the last three blood pressure values of both SBP and DBP during phase II were not significant different between the CFS and the control group. The overshoot of SBP and DBP (phase IV) after the Valsalva maneuver was higher in the CFS patients than in the controls, despite the fact that 14 (38%) CFS patients could not attain an expiratory pressure of 40 mm Hg in contrast to only one subject in the control group.

The heart rate response during mental arithmetic was significantly lower in the CFS patients, although there was a large overlap between the individual values of both groups (Fig. 1). The CFS patients performed as well (20.4 ± 1.2 subtractions) with even less mistakes (3.9 ± 1.7) ($p = 0.03$) than the healthy volunteers (22.6 ± 1.2 subtractions; 4.8 ± 2.0 mistakes). Thus, the mental performance in patients with CFS was as good as in the controls with even less mistakes. This is in agreement with the fact that there was no correlation between the CIS-subscale of reduced concentration and the number of subtractions and mistakes during the mental arithmetic in the CFS group and in the control group. It might be possible that concentration problems lead to a lower hemodynamic response during mental arithmetic. In our study, however, there was no significant correlation between the heart rate response during mental arithmetic and the CIS-subscale of reduced concentration in patients with CFS and control subjects.

Both blood pressure and heart rate responses to isometric handgrip exercise were lower in the CFS group than in the controls. The lower level of muscle exertion that was performed by the CFS patients compared to the controls (18.1 ± 6.7 vs 24.6 ± 8.6 arbitrary units; $p < 0.01$) might result in a lower hemodynamic response to isometric handgrip exercise. This is in agreement with the fact that there was a significant correlation between the hemodynamic responses of the isometric handgrip exercise and the muscle exertion in the group of patients with CFS (delta SBP: $r = 0.58$, $p < 0.001$; delta DBP: $r = 0.68$, $p < 0.001$) and in the control group (delta SBP: $r = 0.34$, $p < 0.05$; delta DBP: $r = 0.36$, $p < 0.05$). After correction for muscle exertion the hemodynamic responses during the handgrip exercise was not significantly different between the two groups (ANCOVA, delta SBP: $p = 0.84$ (NS); delta DBP: $p = 0.68$ (NS)). The average level of reduced motivation (CIS-subscale of reduced motivation), functional impairment (SIP-total) and somatization (SCL-subscale somati-

Table 2. Median (interquartile range) scores of the questionnaires in patients with chronic fatigue syndrome (CFS) and in healthy control group (controls)

	CFS (n = 37)	Controls (n = 38)	p value*
Checklist Individual Strength (CIS)			
CIS-fatigue	53 (49–55)	13 (9.8–18.3)	$p < 0.001$
CIS-concentration	29 (27–34)	7.5 (5–12)	$p < 0.001$
CIS-motivation	16 (11–22.5)	6 (4–9)	$p < 0.001$
CIS-physical activity level	17 (10.5–21)	4 (3–6.3)	$p < 0.001$
Sickness Impact Profile (SIP)			
SIP-home management	238 (152–363)	0 (0–0)	$p < 0.001$
SIP-mobility	168 (106.5–239)	0 (0–0)	$p < 0.001$
SIP-alertness behaviour	384 (296.5–511)	0 (0–0)	$p < 0.001$
SIP-sleep/rest	167 (110–228)	0 (0–0)	$p < 0.001$
SIP-ambulation	144 (86–241)	0 (0–0)	$p < 0.001$
SIP-social interaction	301 (192–420)	0 (0–0)	$p < 0.001$
SIP-work	361 (105.5–361)	0 (0–0)	$p < 0.001$
SIP-recreation and pastimes	223 (149.5–261)	0 (0–0)	$p < 0.001$
SIP-total	1860 (1359–2541)	0 (0–61.5)	$p < 0.001$
Symptom Checklist-90 (SCL-90)			
SCL-anxiety	14 (12–17)	11 (10–12)	$p < 0.001$
SCL-agoraphobia	8 (7–10.5)	7 (7–7.3)	$p < 0.01$
SCL-depression	27 (23–37)	18 (16–20.3)	$p < 0.001$
SCL-somatization	28 (24.5–35)	14 (13–15)	$p < 0.001$
SCL-cognitive difficulties	24 (19.5–27.5)	10 (9–13)	$p < 0.001$
SCL-interpersonal sensitivity	24 (21–28)	21 (19–24.3)	$p < 0.01$
SCL-hostility	8 (6–9.5)	7 (6–7.3)	$p < 0.01$
SCL-sleep	7 (5–10)	3 (3–4)	$p < 0.001$
SCL-total	152 (138–182)	103.5 (96.8–111)	$p < 0.001$

*p values are for the Mann-Whitney rank sum test.

Table 3. Results of the cardiovascular reflex tests in patients with chronic fatigue syndrome (CFS) and in a healthy control group (controls)

	CFS (n = 37)	Controls (n = 38)	p value*
Forced breathing test			
I-E difference	28.4 ± 10.5	32.2 ± 9.5	NS
Standing up test			
t/b ratio	1.5 ± 0.2	1.6 ± 0.3	NS
Delta HR max	37.6 ± 8.9	40.2 ± 8.9	NS
Delta SBP	4.0 ± 10.0	0.6 ± 9.0	NS
Delta DBP	8.1 ± 7.0	6.8 ± 5.7	NS
Valsalva maneuver			
Valsalva ratio	2.0 ± 0.4	1.9 ± 0.4	NS
Lowest SBP during phase IV	121.5 ± 19.9	115.0 ± 20.5	NS
Lowest DBP during phase IV	92.6 ± 16.6	83.2 ± 15.7	$p < 0.05$
SBP at the end of phase IV	137.6 ± 24.6	134.4 ± 24.4	NS
DBP at the end of phase IV	108.0 ± 22.1	101.5 ± 18.9	NS
Delta SBP (phase IV)	39.4 ± 20.6	27.0 ± 18.1	$p < 0.01$
Delta DBP (phase IV)	22.2 ± 10.0	17.3 ± 8.7	$p < 0.05$
Mental arithmetic test			
Delta HR	22.6 ± 9.9	29.5 ± 16.7	$p < 0.05$
Delta SBR	30.1 ± 12.7	30.2 ± 10.1	NS
Delta DBP	18.8 ± 7.4	21.1 ± 6.0	NS
Sustained handgrip exercise			
Delta HR	15.3 ± 8.7	20.2 ± 9.5	NS[1]
Delta SBP	30.4 ± 16.6	36.9 ± 14.9	NS
Delta DBP	19.8 ± 14.8	26.2 ± 10.0	NS[1]

*p values are for the Student's *t*-test or ANCOVA[1]
I-E, inspiration-expiration; t/b, tachycardia/bradycardia; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

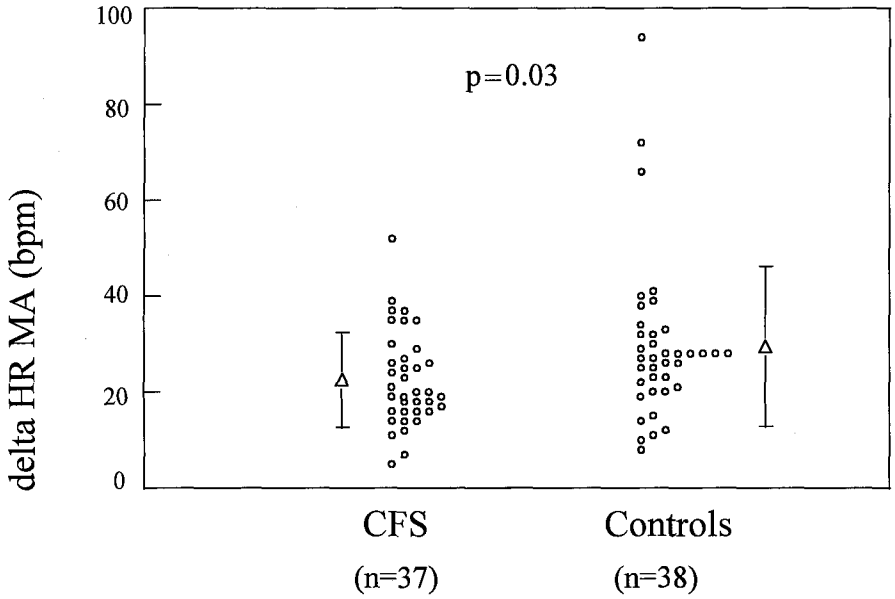

Figure 1. Heart rate responses (delta HR) during mental arithmetic test (MA) in patients with chronic fatigue syndrome (CFS) compared to a healthy control group (controls). p value is for the Student's *t*-test.

zation) was higher in patients with CFS than in controls. It could be hypothesised that this might result in a reduced muscle exertion in patients compared to the controls. In patients with CFS there was, however, no significant correlation between the muscle exertion and the CIS-subscale of reduced motivation, the SIP-total, and the SCL-subscale somatization.

Cardiovascular deconditioning can influence the autonomic nervous function. In our CFS group there was however no correlation between the number of hours patients stayed in bed during 24 hours and the blood pressure response during the Valsalva maneuver and the heart rate response during mental arithmetic.

In addition, the CFS group was devided into a group with three or more autonomic dysfunction complaints (n = 9) and into a group with less than three of such complaints (n = 28). Between these two CFS groups there were no significant differences in age, duration of CFS diagnosis, and the level of fatigue (CIS-fatigue) and functional impairment (SIP-total). Also, the hemodynamic parameters of the five cardiovascular reflex tests were similar in both CFS groups.

Discussion

In this study we compared the autonomic responses to various cardiovascular reflex tests in CFS patients with control subjects' responses. In agreement with several previous studies, many of our CFS patients appeared to have several complaints suggestive of autonomic dysfunction such as increased sweating, dysphagia, and constipation [9,20]. Nevertheless, extensive cardiovascular reflex testing did not disclose definite autonomic dysfunction in this unselected group of CFS patients.

Several other studies assessed the integrity of the autonomic nervous system in CFS patients by different approaches. Some have used postural challange to show that patients with CFS develop hypotension or tachycardia [6–9]. Others have used exercise testing and their data also suggest cardiovascular dysfunction [21,22]. Some could demonstrate a decreased heart rate variability in rest or during paced breathing, using spectral analysis of RR intervals [23–25], reflecting a possible decreased vagal tone. Others could not find a difference in heart rate variability [12,26]. Differences in the used study protocol and in the selection of patients and controls might account for the discrepancies between the different studies. In contrast to some previous studies [6,7,9], the CFS patients in the current study were not selected for having symptoms due to autonomic dysfunction. In the present study we did not find orthostatic hypotension after the patients were standing for 1 minute. Freeman *et al.* [9] also could not demonstrate orthostatic hypotension during active standing in CFS patients. This is in agreement with another study in which active standing for 30 minutes did not elicit orthostatic hypotension in unselected CFS patients [26]. However, using a prolonged tilt table test instead of active standing resulted in orthostatic hypotension after a mean orthostatic period of 15 minutes [6], 16 minutes [10], 19 minutes [11], or 21 minutes [7]. An abnormal response (*e.g.*, [pre]syncope) to head-up tilt without isoproterenol administration occurred in 25% [9], 40% [11], 71% [7], or 100% [8] of the CFS patients. The difference between these studies are most probably due to differences in the selection of CFS patients, definition of an abnormal response to head-up tilt, and the study protocol. For example, the study of Rowe *et al.* [6] included a selected small group of adolescents with chronic fatigue (n = 7) of whom only four patients fulfilled the criteria of CFS. Stewart *et al.* [10] examined children with CFS instead of adults. In addition, differences in used techniques reflect distinctions between the studies. Head-up tilt after fasting, using an intravenous

line insertion, using a larger tilt angle or using infusion of isoproterenol increase the sensitivity but decrease the specificity of the tilt table testing [27]. Some did not exclude patients who used medications influencing the autonomic nervous system [11,23]. Finally, some studies did not include control groups [6,8].

The heart rate response during standing tended to be lower in our CFS group, which was not found in other studies [9,26]. The I-E difference was also slightly decreased, which was also found by Freeman *et al.* [9]. These findings might reflect a tendency of a decreased parasympathetic function or a decreased parasympathetic receptor function in patients with CFS.

The reduced performance of physical tasks explains the reduced blood pressure and heart rate responses during isometric handgrip exercise, but can not explain the increased blood pressure overshoot immediately after stopping the Valsalva maneuver. It could be expected that a lower expiratory pressure during the Valsalva maneuver, as the CFS patients had, would lead to a reduced hemodynamic response to this maneuver. This was not the case in our study. It is unlikely that the inability to sustain an expiratory pressure of 40 mm Hg is caused by a reduced muscle force, because other investigators found normal contractile properties of skeletal muscles in patients with effort syndromes [28,29]. A previous study showed during the Valsalva maneuver only a tendency of a larger blood pressure decline in phase II and a smaller blood pressure overshoot during phase IV [11], while others did only note an increased Valsalva ratio during this manever [9]. In contrast to these studies we did not find a reduced blood pressure or heart rate response to the maneuver.

During the mental arithmetic task, the CFS patients showed an attenuated heart rate response, suggesting decreased efferent sympathetic nerve traffic to the heart. This is in agreement with the findings of Pagani *et al.*, who demonstrated an attenuated increment in low-frequency heart rate variability during mental arithmetic, although inferences from the low-frequency variability with regard to sympathetic activity are controversial [24]. The attenuated heart rate response to mental arithmetic cannot be attributed to a reduced mental performance because the CFS patients performed the calculations as well as the control group and the number of mistakes were even less. Although the CFS patients perceived more concentration problems, as was indicated by the scores of the CIS questionnaire, there was no significant correlation between the number of subtractions and mistakes and the score of the CIS-subscale of reduced concentration.

Since the CFS patients did spend more time in the recumbent position in daily life than controls, slight autonomic changes might be expected due to cardiovascular deconditioning. Previous studies have shown that orthostatic deconditioning results in orthostatic hypotension, an exaggerated tachycardia upon assuming the upright posture, and reduced heart rate variability [30–32]. In our study, the patients did not have a significant decrease in blood pressure response or exaggerated tachycardia on standing. But it should be noted that they stood only for 1 minute. Only the heart rate variability, as measured by the I-E difference, tended to be lower compared to the controls. Also, we could not demonstrate an association between the number of hours that the patients were supine during 24 hours and the hemodynamic responses to the Valsalva maneuver and mental arithmetic. This is in agreement with Bazelmans *et al.*, who could not demonstrate cardiovascular deconditioning in CFS patients compared to healthy controls during maximal exercise test [33].

In conclusion, we could not demonstrate gross abnormalities in autonomic function in unselected patients with CFS using the classical cardiovascular reflex tests. It is possible that these cardiovascular reflex tests are not sufficiently sensitive to pick up subtle signs of autonomic dysfunction. More sensitive and direct measurements of the autonomic activity may be necessary to establish whether slight autonomic dysfunction is involved in CFS.

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