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Elevated Nocturnal Blood Pressure and Heart Rate in Adolescent Chronic Fatigue Syndrome

Short title: Blood pressures and heart rate in CFS

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Abstract

Aim:

To compare ambulatory recordings of heart rate and blood pressure in adolescents with Chronic Fatigue Syndrome (CFS) and healthy controls. We hypothesized both heart rate and blood pressure to be elevated among CFS patients.

Methods:

44 CFS patients aged 12-18 years were recruited from our paediatric outpatient clinic. The controls were 52 healthy adolescents having similar distribution of age and gender. 24-hours ambulatory blood pressure and heart rate was recorded using a validated, portable oscillometric device.

Results:

At night (sleep), heart rate, mean arterial blood pressure and diastolic blood pressure were significantly higher in CFS patients as compared to controls ($p < 0.01$). During daytime, heart rate was significantly higher among CFS patients ($p < 0.05$), whereas blood pressures were equal among the two groups.

Conclusion:

The findings support previous experimental evidence of sympathetic predominance of cardiovascular control in adolescent CFS patients. Also, the findings prompt increased focus on cardiovascular risk assessment, and suggest a possible target for therapeutic intervention.

Keywords: Chronic Fatigue Syndrome; ambulatory blood pressure recording; autonomic nervous system

Chronic Fatigue Syndrome (CFS) is a relatively common and disabling condition among adolescents in developed countries (1,2); recently, the prevalence among 8-17 years olds was reported as high as 1.3 % (3). The disease places a substantial burden on patients, their families and caretakers, and hence on the society.

The pathophysiology of CFS is unknown, but recent evidence suggests that abnormalities of cardiovascular regulation may play an important role. Various forms of orthostatic intolerance have been demonstrated both in adult (4) and pediatric (5-8) patients. A common finding is higher heart rate at rest and a stronger increase in heart rate during orthostatic challenge as compared to controls. In addition, a significant tendency towards higher diastolic and mean blood pressure, both at rest and during mild orthostatic stress, has been noted in experimental studies from our laboratory (7,8). Furthermore, abnormalities in cerebral (9), muscle (10) and skin (11) hemodynamics have been reported in previous studies. Taken together, these observations indicate that CFS is characterized by functional disturbances of the autonomic nervous system affecting cardiovascular regulation. Such disturbances, in turn, might be directly related to clinical symptoms and disability (12)

Despite these experimental findings, there are few systematic studies of ambulatory heart rate and blood pressure in CFS patients. To our knowledge, such studies have never been performed in adolescent CFS patients, despite increasing use of 24-hours ambulatory blood pressure monitoring in paediatric clinical practice (13). However, possible evidence of continuous alterations of heart rate and blood pressure in these patients would increase our understanding of CFS pathophysiology, as well as raise concern about the long-term risk of cardiovascular morbidity.

The aim of this study was to compare 24-hours recordings of heart rate and blood pressure in adolescent CFS patients and healthy controls; we hypothesized both heart rate and blood pressure to be elevated among CFS patients.

Patients and Methods

Study population

Adolescent CFS patients aged 12 – 18 years were consecutively recruited from the Paediatric outpatient clinic, Oslo University Hospital, Norway, which serves 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 (including depression), were ruled out by a thorough and standardized set of investigations at the time of inclusion in this study.

Different case definitions of CFS exist. The frequently used definition from the International Chronic Fatigue Syndrome Study Group (commonly referred to as the Fukuda-definition) requires at least six months of chronic or relapsing fatigue, severely affecting daily activities, as well as more than 4 of 8 specific accompanying symptoms (14). The validity of this definition has been questioned in adults (15) and children (16). Therefore, in this study, three consecutive months of unexplained disabling fatigue was sufficient for inclusion and no accompanying symptoms were required. This approach is in line with the clinical recommendations from The Royal College of Paediatrics and Child Health (2) and the National Institute for Health and Clinical Excellence (17), and is also proven feasible in previous studies from our group (7, 8, 11).

Healthy control subjects volunteered from schools in two neighboring Norwegian cities. A recruiting process was established that assured the control and patient groups to have an equal distribution of age, sex and ethnicity. Control subjects reporting a chronic disease or using drugs (including contraceptive pills) on a regular basis were excluded.

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

Recording of ambulatory blood pressure and heart rate

24-hours ambulatory blood pressure and heart rate was recorded using a validated, portable oscillometric device (Oscar2, SunTech Medical, Morrisville, NC, USA) (18). Patients and controls underwent identical assessment protocols; an appropriate arm cuff was chosen from two different cuff sizes available (adult and large adult) and attached to the non-dominant arm. Participants were instructed to relax the arm and keep it alongside the trunk during daytime measurements. The device was programmed to measure blood pressure and heart rate every 20 minutes during daytime and every 30 minutes at night; night-time (sleep) was individually adjusted according to information given by each participant.

For CFS patients, measurements were performed in relation to a two-day clinical investigation program, often implying overnight stay at an accommodation service attached to the hospital. For healthy controls, measurements were performed at home, thus including a regular school day (occasionally with physical education lessons) as well as normal afternoon leisure activities, such as sports and social activities. However, all healthy controls were instructed to avoid strenuous exercise during the recording period.

Data analyses

The validity of each blood pressure/heart rate measurement was automatically evaluated by the monitoring device. For each participant, a minimum of 40 valid measurements (at least 8 of them during night-time) were required for the entire recording to be valid. Each recording was retrieved by manufacturer developed software (AccuWin Prov3, SunTech Medical, Morrisville, NC, USA), and thereafter exported to Excel 2003/2007 (Microsoft Office, Redmond, Washington, USA).

The statistical analyses were performed using SPSS version 17 (SPSS inc., Chicago, Illinois, USA). Comparison of ambulatory measurements between CFS patients and controls were carried out separately for daytime, nighttime and the entire 24-hours recording period. By inspection of plots, all variables were considered to be normally distributed.

T-tests (two-sided) were used to compare means in the two groups. Multivariate linear regression analyses were carried out to control for a potential confounding effect of different BMI in the two groups. A significance level of 5 % was used throughout.

Results

53 CFS patients were eligible for the study. Among these, six patients were excluded because ambulatory recordings were not carried out according to protocol, and three were excluded due to non-valid measurements, leaving 44 for the final analyses. The patients reported severe functional impairments; they were physically inactive, did

not participate in leisure activities and had a high level of school absence. However, no one was permanently bedridden. Disease duration at the time of referral varied from 3 months to 5-6 years.

54 healthy controls were enrolled. However, one was excluded due to non-Caucasian ethnicity, and one was excluded due to non-valid measurement, leaving 52 for the final analyses. The controls were appraised to have normal levels of activity for their age. Some participated in sports, but no one was top athletes; some preferred a more sedentary life style, but not to any extreme extent. There were no significant demographic or biometrical differences between the two groups except for BMI ($p = 0.046$) (Table 1).

At night (sleep), heart rate (HR), diastolic blood pressure (DBP) and mean arterial blood pressure (MAP) were significantly higher in CFS patients as compared to controls. Systolic blood pressure (SBP) was equal among the two groups. At daytime, HR was significantly higher among CFS patients, but blood pressures were equal among the two groups (Table 2). These differences remained when controlling for the possible confounding effect of BMI in multivariate analyses.

Discussion

The most important findings in our study are the elevated HR and blood pressure among CFS patients at night and the elevated HR during daytime. Our HR results are in line with a population based study on adult CFS patients (19), whereas our blood pressure results contrast a recent report on lower ambulatory blood pressure among CFS adults (20). The latter discrepancy might be explained by differences in population (age group, duration of disease) and methodology.

Our findings might have consequences for the understanding of disease mechanisms, risk assessment and treatment options. Concerning disease mechanisms, this study contributes to the growing evidence of altered autonomic cardiovascular regulation in CFS. During head-up tilt-test and similar experiments, CFS patients are characterized by higher resting HR, MAP and DPB as compared to controls, and a stronger increase in these variables upon orthostatic challenge (7,8). Of note, no differences were found for SBP. These findings have been interpreted as indicating a sympathetic predominance of cardiovascular control, which however might be attributed to stress in the experimental situation. The results of the present study comply neatly with these experimental findings, suggesting that sympathetic predominance in CFS might be a more permanent feature, affecting cardiovascular control in daily life. Thus, our results support a theory of permanent stress responses ("sustained arousal") as a fundamental aspect of CFS disease mechanisms (21).

As for risk assessment, elevated nocturnal blood pressure might be the first sign of developing primary hypertension, and is a well-established risk factor for long-term cardiovascular morbidity (22). Our results should prompt exploration of other cardiovascular risk factors among CFS patients (such as genetic markers and lipid profile), as well as epidemiological studies of cardiovascular events. Clinically, regular blood pressure check-ups of individual patients seem to be warranted. As outlined below, we cannot rule out that the tendency towards higher heart rate and blood pressure among CFS patients might be due to inactivity rather than being a primary effect of their disease. This uncertainty, however, does not necessarily weaken the concerns related to long-term cardiovascular risk. Indeed, a growing body of evidence suggests that physical inactivity in adolescence is related to obesity, insulin resistance and other well-established risk factors of cardiovascular diseases in later life (23)

Concerning treatment options, the putative role of sympathetic predominance in CFS pathophysiology constitutes a possible target for pharmacological intervention; such intervention might improve the clinical condition as well as increase the understanding of underlying disease mechanisms. There are case reports of beneficial effects of beta-blocker treatment in adolescent CFS (24). However, no systematic trials have been carried out.

Study limitations

The case definition of CFS in adolescents is disputed. This study applied a modification of the Fukuda-definition, and our results cannot be readily compared with studies adhering strictly to this definition. Our approach is likely to improve the generalizability of the results towards routine clinical care, though, as our case definition is in line with authoritative clinical recommendations (2, 17). Also, using a broad case definition should increase the risk of type II errors; thus, criticism of this approach seems to be more relevant towards reports of negative findings.

The ambulatory recordings of CFS patients were performed during the two-day clinical investigation program which often included overnight stay at an accommodation service, whereas the controls were examined at home carrying out ordinary activities. Thus, we cannot exclude the possibility of systematic errors. For instance, a strange sleeping environment combined with psychological stress related to the hospital visit might have contributed to elevated heart rate and blood pressure in the CFS group. Unfortunately, we have no data on sleeping quality during the recording period. On the other hand, having no activity restrictions (except from avoiding strenuous exercise) in the control group should have had the opposite effect, i.e. elevated heart rate and blood pressure among controls.

Furthermore, CFS patients were more sedentary than controls, possibly constituting another confounding factor. However, no one was permanently bedridden; in addition, physical activity is shown to be responsible for only a small part of diurnal variation in heart rate and blood pressure (25). Unfortunately, we did not conduct any formal assessment of activity level. Neither did we perform any exercise tolerance tests to evaluate cardiorespiratory capacity. The latter, however, might be considered inadequate in CFS patients: First, as previous studies have provided evidence of altered short-time autonomic cardiovascular control in CFS patients during orthostasis and isometric exercise (4-8), we find it likely that the cardiovascular control during dynamic exercise might be altered as well. Thus, it seems difficult to tell whether any deviations from normal cardiorespiratory responses during exercise tolerance tests are due to an underlying autonomic dysregulation or another factor (such as sedateness). Second, exercise tolerance tests often imply a gradual increase in strain until the level of exhaustion. As CFS patients regularly report deterioration of their symptoms and functional level long after strenuous exercise, such test might be considered inappropriate.

Concluding remarks

The findings of this study support previous evidence of sympathetic predominance in adolescent CFS patients, rise concerns about long-term cardiovascular risks and suggest a possible target for therapeutic intervention. Further studies should consider comparing CFS patients with other patient groups suffering from immobilization. In addition, they should address whether CFS patients have altered sleeping patterns which in turn might influence their blood pressure control.

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Tables

Table 1. Subject characteristics

	CFS patients	*Controls*	*P – value**
Number	44	52	
Girls (%)	32 (73%)	35 (67%)	NS
Mean age, years (SD)	15 (1.7)	15 (1.6)	NS
Mean weight, kg (SD)	62 (15.1)	59 (11.2)	NS
Mean height, cm (SD)	166 (9.3)	168 (9.1)	NS
Mean BMI (SD)	22.5 (4.6)	20.7 (2.6)	**0.046**

*T-test (2-sided)
SD = Standard Deviation; BMI = Body Mass Index; CFS = Chronic Fatigue Syndrome; NS = Not Significant

Table 2. 24-hours ambulatory recordings of blood pressure and heart rate. Mean (SD)

	CFS patients (n=44)	*Controls (n=52)*	*P-value**
SBP awake (mmHg)	120.0 (10.2)	122 (8.2)	0.083
SBP asleep (mmHg)	110.8 (10.0)	107.3 (8.9)	0.130
SBP total (mmHg)	118.2 (9.9)	118.3 (8.3)	0.651
DBP awake (mmHg)	69.2 (7.5)	70.1 (4.0)	0.329
DBP asleep (mmHg)	57.9 (5.8)	53.7 (4.2)	**< 0.001**
DBP total (mmHg)	66.8 (7.0)	65.4 (4.0)	0.651
MAP awake (mmHg)	86.0 (8.0)	87.7 (4.9)	0.124
MAP asleep (mmHg)	75.5 (6.6)	71.6 (5.3)	**0.007**
MAP total (mmHg)	84.0 (7.6)	83.1 (5.0)	0.732
HR awake (beats/min)	80 (10)	76 (8)	**0.026**
HR asleep (beats/min)	68 (9)	63 (9)	**0.004**
HR total (beats/min)	77 (9)	72 (8)	**0.004**

* Multivariate linear regression, adjusted for BMI
BMI = body mass index; CFS = chronic fatigue syndrome; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial blood pressure; HR = heart rate; SD = Standard Deviation