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# Abnormal Thermoregulatory Responses in Adolescents With Chronic Fatigue Syndrome: Relation to Clinical Symptoms

Vegard Bruun Wyller, MD<sup>a,b</sup>, Kristin Godang, BSc<sup>c</sup>, Lars Mørkrid, MD, PhD<sup>d</sup>, Jerome Philip Saul, MD<sup>e</sup>, Erik Thaulow, MD, PhD<sup>a</sup>, Lars Walløe, MD, PhD<sup>b</sup>

Departments of <sup>a</sup>Pediatrics, <sup>c</sup>Endocrinology, and <sup>d</sup>Medical Biochemistry, Rikshospitalet-Radiumhospitalet Medical Center, Oslo, Norway; <sup>b</sup>Department of Physiology, University of Oslo, Oslo, Norway; <sup>e</sup>Department of Pediatrics, Medical University of South Carolina, Charleston, South Carolina

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## ABSTRACT

**OBJECTIVES.** Chronic fatigue syndrome is a common and disabling disease of unknown etiology. Accumulating evidence indicates dysfunction of the autonomic nervous system. To further explore the pathophysiology of chronic fatigue syndrome, we investigated thermoregulatory responses dependent on catecholaminergic effector systems in adolescent patients with chronic fatigue syndrome.

**PATIENTS AND METHODS.** A consecutive sample of 15 patients with chronic fatigue syndrome aged 12 to 18 years and a volunteer sample of 57 healthy control subjects of equal gender and age distribution were included. Plasma catecholamines and metanephrines were measured before and after strong cooling of 1 hand. Acral skin blood flow, tympanic temperature, heart rate, and mean blood pressure were measured during moderate cooling of 1 hand. In addition, clinical symptoms indicative of thermoregulatory disturbances were recorded.

**RESULTS.** Patients with chronic fatigue syndrome reported significantly more shivering, sweating, sudden change of skin color, and feeling unusually warm. At baseline, patients with chronic fatigue syndrome had higher levels of norepinephrine, heart rate, epinephrine, and tympanic temperature than control subjects. During cooling of 1 hand, acral skin blood flow was less reduced, vasoconstrictor events occurred at lower temperatures, and tympanic temperature decreased more in patients with chronic fatigue syndrome compared with control subjects. Catecholamines increased and metanephrines decreased similarly in the 2 groups.

**CONCLUSIONS.** Adolescent patients with chronic fatigue syndrome have abnormal catecholaminergic-dependent thermoregulatory responses both at rest and during local skin cooling, supporting a hypothesis of sympathetic dysfunction and possibly explaining important clinical symptoms.

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### Key Words

chronic fatigue, thermal regulation, adolescents, pathogenesis

### Abbreviations

CFS—chronic fatigue syndrome  
AVA—arteriovenous anastomosis  
CDC—Centers for Disease Control and Prevention  
ASBF—acral skin blood flow  
TT—tympanic temperature  
HR—heart rate  
MBP—mean blood pressure  
CI—confidence interval

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Address correspondence to Vegard Bruun Wyller, MD, Department of Pediatrics, Rikshospitalet-Radiumhospitalet Medical Center, N-0027 Oslo, Norway. E-mail: [brwyll@online.no](mailto:brwyll@online.no)

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**C**HRONIC FATIGUE SYNDROME (CFS) is a disabling disease that affects people worldwide.<sup>1</sup> The etiology remains unknown. However, there is accumulating evidence of orthostatic intolerance and other disturbances of cardiovascular regulation in this patient group.<sup>2-4</sup> Dysfunction of the autonomic nervous system, and particularly the sympathetic branch, has, therefore, been proposed as an important component of the pathophysiology.<sup>5,6</sup> Notably, the autonomic nervous system also has an essential role in human thermoregulation.<sup>7</sup> However, this regulatory function has hardly been explored in CFS despite frequent complaints of fever-like sensation, night sweats, and subjective temperature sensitivity (feeling too hot or cold).<sup>1,8</sup>

Human thermoregulation involves complex control mechanisms. Discrete regions of the hypothalamus are sensitive to changes in core body temperature; in addition, these regions receive afferent information from peripheral thermoreceptors.<sup>7,9</sup> The main effector organs are skeletal muscles, sweat glands, skin arterioles, and skin arteriovenous anastomoses (AVAs). Skeletal muscles are controlled by motor neurons of the somatic nervous system; however, enhanced sympathetic outflow and epinephrine secretion promote shivering.<sup>7,9</sup> Sweat glands are innervated by cholinergic sympathetic neurons, which also seem to promote vasodilation in nearby arterioles by local release of nitric oxide and prostaglandins from endothelial cells.<sup>10,11</sup> In addition, skin arterioles are controlled by vasoconstrictive noradrenergic sympathetic neurons.<sup>9</sup> The AVAs, of which their presence seem to be confined to acral, glabrous skin areas (eg, the palms and soles),<sup>12</sup> receive noradrenergic sympathetic efferents only; thus, AVA blood flow fluctuations reflects sympathetic nerve activity.<sup>13</sup> Although AVAs are influenced by local factors as well, previous experiments in our laboratory indicate that they are under strong central control and that they play an important part in overall thermoregulation.<sup>14,15</sup>

The aim of this study was to explore aspects of thermoregulation in adolescent patients with CFS. Because CFS has been linked to sympathetic dysfunction,<sup>5,6</sup> we specifically focused on catecholaminergic-dependent effector systems and hypothesized to find differences between patients with CFS and healthy control subjects both at rest and during local skin cooling.

## PATIENTS AND METHODS

### Subjects

Patients with CFS aged 12 to 18 years were consecutively recruited from the outpatient clinic at the Department of Pediatrics, Rikshospitalet-Radiumhospitalet Medical Center, 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.<sup>8</sup> Different case definitions of CFS exist. This study adhered to all of the main criteria in the definition from the Centers for Disease Control and Prevention (CDC).<sup>16</sup> Specifically, we required  $\geq 6$  months of chronic or relapsing fatigue, severely affecting daily activities; the fatigue should not be explained by any concurrent condition, it should be new or definite in onset, it should not be related to ongoing exertions, and it should not be alleviated by rest. In addition, according to the CDC definition, the patients are also required to report  $\geq 4$  of 8 specific accompanying symptoms (headache, muscle pain, joint pain, sore throat, tender lymph nodes, impaired memory/concentration, unrefreshing sleep, and postexertional malaise). However, the validity of this last demand has been questioned, both in pediatric<sup>17</sup> and adult<sup>18</sup> patients. Indeed, recent evidence, as reviewed by Cho et al,<sup>19</sup> raises serious concerns about this part of the CDC definition. Therefore, accompanying symptoms were not required in this study.

Healthy control subjects aged 12 to 18 years volunteered from local schools. The recruiting procedure assured an equal distribution of age and gender among patients and control subjects. A high number of participants in both groups would have yielded best statistical power. However, because control subjects were far easier to recruit than patients with CFS, we aimed at an  $\sim 4:1$  relation. Subjects having a chronic disease (such as allergy, skin diseases, vascular diseases, or diabetes) or using drugs (including contraceptive pills) on a regular basis were excluded.

One week before the experiments, all of the 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 instructed to have fasted overnight.

Written informed consent was obtained from all of the 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 autonomic dysfunction,<sup>20</sup> was translated into Norwegian by Dr Wyller and slightly modified to fit our particular age group. A couple of items in this questionnaire are specifically directed toward sudomotor and vasomotor function, which, in turn, is related to mechanisms of thermoregulation. The subjects answered by interview.

### Neuroendocrine Responses to Strong Cooling

The experimental part of this study was undertaken at the Department of Pediatrics, Rikshospitalet-Radiumhospitalet Medical Center and was performed during the

same day in each participant. The first set of experiments began at 8:00 AM and was conducted in a quiet room with normal ambient temperature. The subjects were instructed to apply an ointment containing the local anesthetic lidocaine (eutectic mixture of local anesthetic) on the skin of the antecubital fossa 1 hour in advance. They rested supine for ~15 minutes, and a catheter was then placed in an antecubital vein. After supine rest for another 15 minutes, blood samples were collected on ice-cold Vacutainer tubes containing glutathione-ethylene glycol tetraacetic acid and heparin for measurements of plasma catecholamines (norepinephrine, epinephrine, and dopamine) and metanephrines (normetanephrine, metanephrine, and 3-methoxytyramine), respectively. The opposite hand was then immersed in cold water (10°C) for 2 minutes, after which new blood samples were collected immediately. Samples were then centrifuged at 4°C, and plasma was separated for storage at -80°C until assayed.

Metanephrines were extracted from plasma using solid-phase ion exchange columns (Bond Elute-Accucat; Varian Medical Systems, Palo Alto, CA) and a commercial mobile phase (Chromsystems, München, Germany).<sup>21</sup> Both catecholamines and metanephrines were quantified by high-performance liquid chromatography with a reverse-phase column and glassy carbon electrochemical detector (Agilent Technologies, Colorado Springs, CO). The intraassay and interassay variations were 10.7% and 14.5% for norepinephrine, 23.5% and 10.5% for epinephrine, 7.2% and 6.8% for dopamine, 12.6% and 4.3% for normetanephrine, 11.7% and 3.0% for metanephrine, and 15.3% and 11.2% for 3-methoxytyramine, respectively.

### Cardiovascular Responses to Moderate Cooling

The second set of experiment started at 2:00 PM. The participants had been offered a standardized, light meal (2 pieces of bread, 1 glass of juice) 1 hour before but were otherwise not allowed to eat or drink. They were lightly dressed and lay supine in a climatic chamber. The ambient temperature was maintained at ~26°C, assuring that subjects were within their thermoneutral zone. The left hand was immersed in a stirred thermostat-controlled water bath (CB 29-20e; Heto-Holtan, Åbyhøj, Denmark) with a temperature of 35°C, which corresponds with thermoneutrality in water. Thirty minutes were used for acclimatization and another 5 minutes for baseline registration, after which the water temperature was gradually lowered to 19°C over ~50 minutes (Fig 1).

Continuous recordings of acral skin laser flux, which is a measure of acral skin blood flow (ASBF), were obtained by a laser-Doppler instrument (DRT4; Moore Instruments, Milway, Devon, United Kingdom).<sup>22</sup> The probes, which function equally well under water,<sup>23</sup> were firmly attached with adhesive strips to the pulp of the

flexor surface of the distal phalanges of the right and left index finger. In this position, the probes mainly detect blood flow in AVAs, as has been shown in earlier experiments in our laboratory.<sup>22,23</sup> Tympanic temperature (TT) was continuously monitored by an electronic probe (D-TM1; Exacon, Roskilde, Denmark) inserted in the outer auditory canal and isolated from the ambient air by a piece of cotton. TT corresponds well with core body temperature.<sup>24</sup> Instantaneous heart rate (HR) was obtained from the R-R interval of the electrocardiogram. Photoplethysmography on the right third finger was used to obtain a noninvasive, continuous recording of arterial blood pressure (2300 Finapres; Ohmeda, Madison, WI). This method correlates satisfactorily with invasive pressure measurements<sup>25</sup> and has also been validated in adolescents and children.<sup>26</sup>

All of the recorded signals, including the temperature of the water bath, were transferred online to a recording computer running a program for real-time data acquisition (developed by Morten Eriksen, Department of Physiology, University of Oslo, Oslo, Norway). Beat-to-beat mean blood pressure (MBP) was calculated by numerical integration of the recorded instantaneous blood pressure. The other physiologic variables were also converted to beat-to-beat records.

### Data Analysis

Data were exported to Microsoft Excel (Microsoft, Redmond, WA) for further calculations. For the strong-cooling experiments,  $\Delta$  cooling (postcooling - precooling) was computed for each variable. For the moderate-cooling experiments, the beat-to-beat records of each variable were used to find the median value (of 100 consecutive heart beats) at 35°C water temperature (precooling), 27°C water temperature (early cooling), and 19°C water temperature (late cooling).  $\Delta$  cooling 1 (early cooling - precooling) and  $\Delta$  cooling 2 (late cooling - precooling) was also computed for each variable.

During moderate cooling, ASBF in the cooled hand usually ceases quite suddenly, probably reflecting a coordinated closure of the AVAs<sup>23</sup> (Fig 1). In each subject, this vasoconstrictor event was defined to occur at the water temperature where the median value of ASBF left (computed over 30 consecutive heart beats) was permanently <50% of the median value before cooling.

The statistical analyses were conducted by using SPSS statistical software (SPSS Inc, Chicago, IL). On the basis of inspection of plots, most variables were appraised not to follow a normal distribution, and experimental results are, therefore, expressed as medians with nonparametric 95% confidence intervals (CIs) (Tables 3 and 4). The vasoconstrictor events in the moderate-cooling experiments were subjected to "survival analysis" using a Kaplan-Meier plot (Fig 2). Fisher's exact test, Wilcoxon-Mann-Whitney's test, and log rank test (all 2-sided) were used to explore differences between the 2 groups.

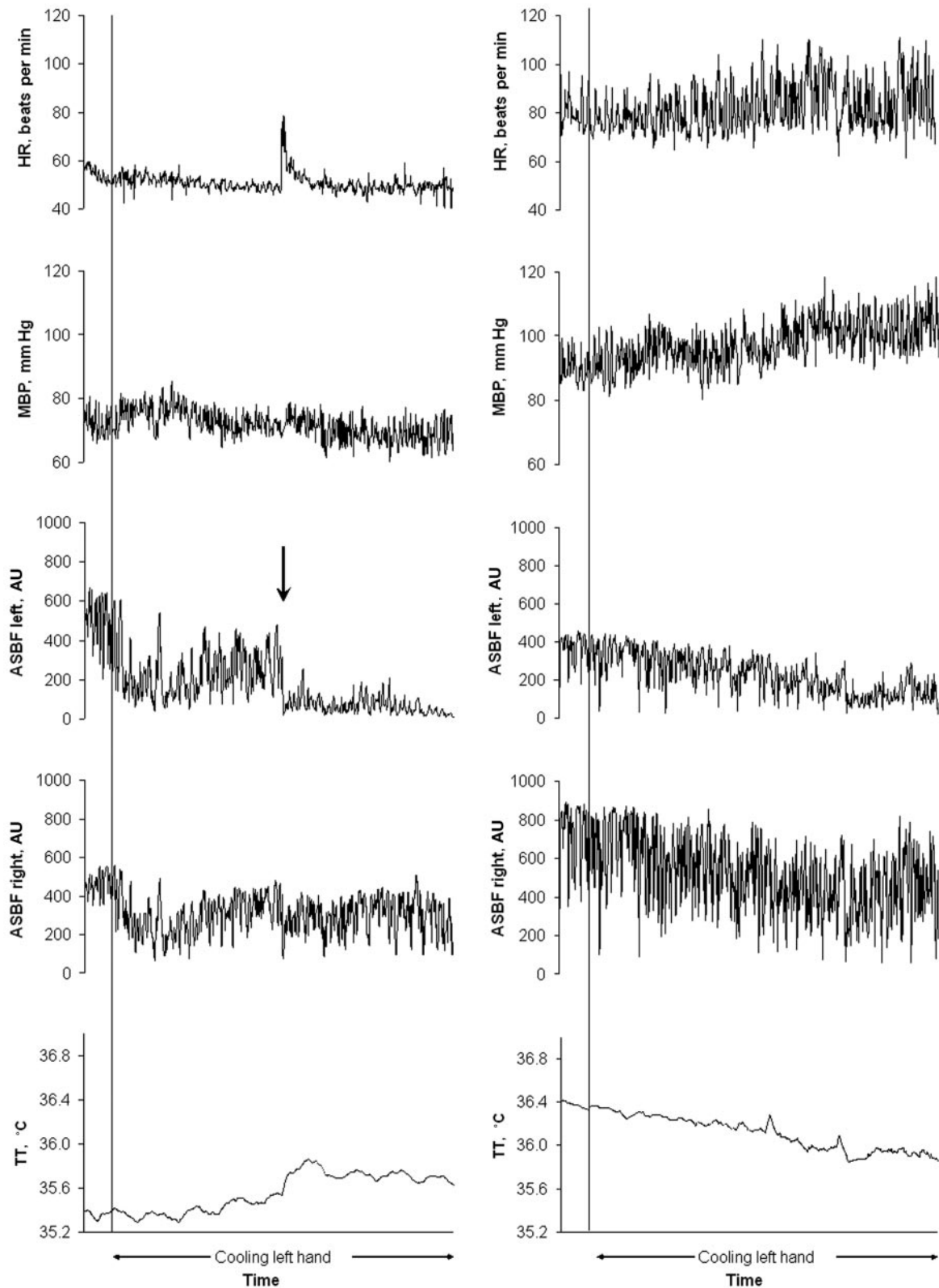
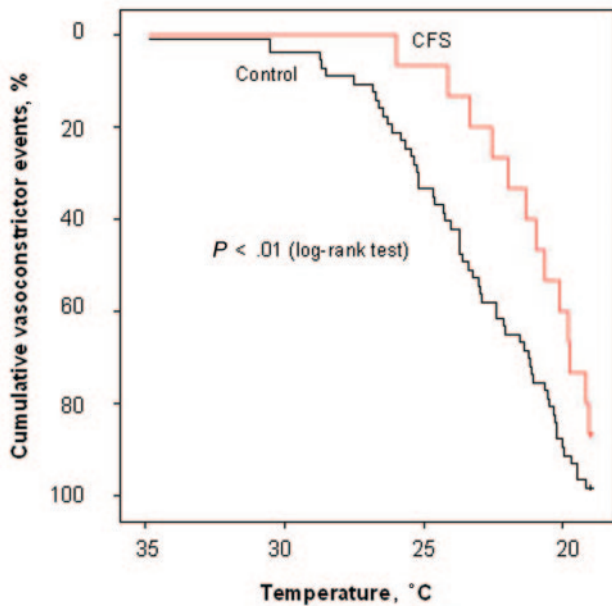


FIGURE 1

Original recordings of data from 1 control subject (left) and 1 patient with CFS (right) during the moderate-cooling experiments. AU indicates arbitrary units. The vertical lines indicate initiation of cooling from 35°C to 19°C of the left hand. Artifacts in the records have been manually removed and replaced by values obtained by linear interpolation. Note the well-defined vasoconstrictor event in the control subject (arrow).<sup>15</sup> This phenomenon is accompanied by a slight, sustained increase in TT (lower), probably caused by the cessation of blood flow to cold skin areas and, thus, reduced heat loss. Simultaneously, there is a transient increase in HR (top), which might be because of a transient increase in cardiac sympathetic outflow. In the patient with CFS, there is no well-defined vasoconstrictor event, and TT fell almost linearly toward the end of the experiment.



**FIGURE 2**  
Kaplan-Meier plot of vasoconstrictor events (sudden cease of ASBF in left hand) in control subjects (black) and patients with CFS (red) during moderate cooling of the left hand. The symbol "+" in the graphs represents censored individuals (2 patients and 1 control subject), meaning that a vasoconstrictor event never occurred.

A  $P \leq .05$  was considered statistically significant. To reduce the methodologic problem of multiple comparisons, statistical tests were only performed for the variables precooling and  $\Delta$  cooling 2 (Tables 3 and 4). Among these variables, the changes in norepinephrine, epinephrine, ASBF left, and TT were considered most central to our research questions.

## RESULTS

A total of 15 patients with CFS and 57 healthy control subjects were included in the study (Table 1). The 2 groups were comparable regarding gender, age, weight, and height. All were of white ethnicity, except 1 control subject. Mean duration of fatigue among the patients was 31 months.

The patients with CFS reported significantly more shivering, sweating, and feeling unusually warm (Table 2). They also experienced sudden paleness of skin more often than control subjects, whereas sudden redness of skin was less common in the patient group.

**TABLE 1 Subject Characteristics**

Variable	Control Subjects (N = 57)	Subjects With CFS (N = 15)
Female gender, n (%)	34 (59.6)	10 (66.7)
Age, mean (range), y	15.6 (13–18)	15.1 (12–18)
Weight, mean (range), kg	61.6 (44–99)	59.1 (43–92)
Height, mean (range), cm	171.4 (149–195)	171.4 (160–192)
Duration of fatigue, mean (range), mo	NA	31.1 (6–60)

NA indicates not applicable.

Before strong cooling, patients with CFS had significantly higher levels of norepinephrine ( $P \leq .01$ ) and epinephrine ( $P \leq .05$ ) than control subjects (Table 3). There were no differences in the levels of dopamine and metanephrines (normetanephrine, metanephrine, and 3-methoxytyramine). During strong cooling of the opposite hand, levels of norepinephrine and epinephrine increased in both groups, whereas levels of normetanephrine and metanephrine decreased in both groups. However, all of the variables changed similarly, thus not altering the differences already present at baseline.

Before moderate cooling, patients with CFS had higher HR ( $P \leq .01$ ) and TT ( $P \leq .05$ ) than control subjects (Table 4). There was also a tendency toward lower ASBF in both hands, although this was not significant. During cooling of the left hand, ASBF left decreased significantly less in patients with CFS than in control subjects ( $P \leq .01$ ; Table 4 and Fig 1). Thus, at late cooling, patients with CFS tended to have higher ASBF left than control subjects. Accordingly, the vasoconstrictor events occurred at lower temperatures in patients with CFS than in control subjects ( $P \leq .01$ ; Fig 2). The same tendency, although not significant, was observed for ASBF right. With cooling, TT decreased significantly among patients with CFS but remained stable among control subjects ( $P \leq .05$ ), nullifying the differences present at baseline (Table 4 and Fig 1). HR and MBP remained stable in both groups throughout the experiment.

## DISCUSSION

The most important findings of this study are that (1) patients with CFS report several symptoms that might indicate thermoregulatory disturbances; (2) at baseline, patients with CFS have higher levels of norepinephrine and epinephrine and higher TT than control subjects; and (3) during cooling of 1 hand, the neuroendocrine responses are similar in the 2 groups, but ASBF is less reduced among patients with CFS, whereas the baseline differences in TT disappear. Furthermore, the relevance of these findings is strengthened by the strikingly homogeneous responses within the CFS group, creating significant differences from control subjects despite the small number of subjects studied.

### Baseline Observations

The finding in this study of increased norepinephrine levels in patients with CFS seems to be novel, whereas increased levels of epinephrine have been reported sporadically.<sup>27,28</sup> A higher level of acute emotional stress among patients with CFS might explain the epinephrine differences; however, plasma levels of norepinephrine are less influenced by such mechanisms.<sup>7</sup> Thus, the findings seem to indicate a more substantial alteration of physiology.

A high level of norepinephrine in the antecubital vein

**TABLE 2 Symptoms Indicative of Thermoregulatory Disturbances**

Variable	Control Subjects		Subjects With CFS	
	n/N	%	n/N	%
Experience of sudden changes in skin color	42/57	73.7	15/15	100.0 <sup>a</sup>
Redness of skin	37/42	88.1	7/15	46.7 <sup>b</sup>
Paleness of skin	22/42	52.4	14/15	93.3 <sup>b</sup>
Experience of shivering hands	8/56	14.0	8/15	53.3 <sup>b</sup>
Sweating more than others <sup>c</sup>	4/44	9.1	6/13	46.2 <sup>b</sup>
Feeling unusually warm				
After standing upright for a long period	6/56	10.7	7/14	50.0 <sup>b</sup>
After moderate physical exercise	26/55	47.3	12/15	80.0 <sup>a</sup>
After a hot bath or shower	22/56	39.3	8/15	61.5

<sup>a</sup>  $P \leq .05$ , using Fisher's exact test.<sup>b</sup>  $P \leq .01$ , using Fisher's exact test.<sup>c</sup> This question was added during the course of the study, which explains the lower totals.**TABLE 3 Catecholamines and Metanephrines Before and After Strong Cooling of 1 Hand**

Variable	Precooling, Median (95% CI)		Postcooling (10° C Water), Median (95% CI)		Δ Cooling, Median (95% CI)	
	Control Subjects	Subjects With CFS	Control Subjects	Subjects With CFS	Control Subjects	Subjects With CFS
Norepinephrine, pmol/L	1156 (966 to 1434)	1647 <sup>a</sup> (1478 to 1912)	1494 (1213 to 1807)	2077 (1827 to 2676)	221 (149 to 352)	354 (171 to 671)
Epinephrine, pmol/L	171 (147 to 192)	216 <sup>b</sup> (161 to 273)	209 (193 to 220)	236 (157 to 380)	25 (5 to 46)	9 (-18 to 113)
Dopamine, pmol/L	130 (112 to 151)	157 (121 to 207)	147 (128 to 172)	174 (111 to 224)	13 (-1 to 22)	4 (-33 to 65)
Normetanephrine, nmol/L	0.45 (0.37 to 0.55)	0.36 (0.21 to 0.49)	0.28 (0.23 to 0.40)	0.21 (0.17 to 0.35)	-0.11 (-0.13 to -0.06)	-0.12 (-0.19 to -0.05)
Metanephrine, nmol/L	0.30 (0.27 to 0.34)	0.34 (0.20 to 0.41)	0.25 (0.19 to 0.27)	0.18 (0.13 to 0.35)	-0.05 (-0.09 to -0.01)	-0.05 (-0.15 to -0.02)
3-Methoxytyramine, nmol/L	0.08 (0.07 to 0.09)	0.10 (0.06 to 0.13)	0.08 (0.05 to 0.09)	0.09 (0.04 to 0.12)	0.00 (-0.01 to 0.01)	-0.01 (-0.04 to 0.01)

Blood samples were not obtained from 3 control subjects because of technical difficulties. To reduce the methodologic problem of multiple comparisons, statistical tests were only performed for the variables precooling and Δ cooling.

<sup>a</sup>  $P \leq .01$  for differences between groups, using Wilcoxon-Mann-Whitney's test.<sup>b</sup>  $P \leq .05$  for differences between groups, using Wilcoxon-Mann-Whitney's test.

plasma might suggest increased sympathetic nerve activity to forearm skin and skeletal muscle.<sup>29</sup> Likewise, a high plasma level of epinephrine might be a result of increased sympathetic nerve activity to the adrenals. However, there are several alternative explanations. Generally, high levels of plasma catecholamines could result from either increased spillover or reduced removal, which, in turn, depends on both sympathetic nerve activity, the capacity of different reuptake and breakdown pathways, and local blood flow.<sup>7,29</sup> Furthermore, a high norepinephrine concentration in forearm venous blood might simply reflect increased arterial levels, which, in turn, could be because of enhanced spillover in other parts of the body.

The plasma levels of metanephrines are not good markers of activity in either the adrenal medulla or the sympathetic neurons and are only weakly correlated with the plasma levels of the respective catecholamines.<sup>7,29</sup> Thus, similar levels of metanephrines among patients with CFS and control subjects do not rule out a state of catecholamine excess in the former.

The finding of increased TT in patients with CFS is in agreement with previous reports of increased skin temperature in this population<sup>30</sup> but contrasts with 2 other studies that did not find any deviations in core body temperature.<sup>31,32</sup> However, these latter studies focused primarily on alterations in circadian temperature rhythms. In this study, the increased TT might be partially caused by high levels of epinephrine, which increase basal metabolic rate and heat production.<sup>7</sup> In addition, a tendency toward shivering, as reported in our patients with CFS, might contribute. Increased levels of thyroid hormone are an alternative explanation that has not been specifically addressed in this study; however, overt thyroid hyperfunction was ruled out in the patient group during routine clinical investigations.

The high resting HR found in this study fits well with other studies, documenting similar hemodynamic abnormalities both at rest and during orthostatic stress.<sup>3,33</sup> An abnormal sympathetic predominance of cardiovascular regulation is one possible interpretation of these results, which is consistent with the reduced ASBF

**TABLE 4 Thermoregulatory Variables Before and After Moderate Cooling of Left Hand**

Variable	Precooling (35° C Water), Median (95% CI)		Early Cooling (27° C Water), Median (95% CI)		Δ Cooling 1, (Early Cooling — Precooling), Median (95% CI)		Late Cooling (19° C Water), Median (95% CI)		Δ Cooling 2 (Late Cooling — Precooling), Median (95% CI)	
	Control Subjects	Subjects With CFS	Control Subjects	Subjects With CFS	Control Subjects	Subjects With CFS	Control Subjects	Subjects With CFS	Control Subjects	Subjects With CFS
HR, beats per min	70.7 (67.7 to 73.8)	80.3 (66.1 to 91.2) <sup>a</sup>	69.5 (65.2 to 72.9)	77.7 (70.3 to 89.9)	-1.6 (-5.1 to 1.0)	-2.3 (-17.2 to 7.4)	73.5 (68.5 to 76.6)	79.0 (69.0 to 91.1)	1.3 (-1.0 to 2.3)	-0.1 (-10.8 to 10.6)
MBP, mm Hg	81.7 (78.2 to 86.0)	84.0 (74.4 to 93.6)	80.6 (78.2 to 86.0)	85.6 (78.0 to 89.6)	-0.6 (-5.0 to 3.7)	2.0 (-8.0 to 6.0)	85.2 (79.2 to 88.6)	83.1 (77.7 to 99.5)	2.5 (0.6 to 4.8)	2.1 (-4.3 to 10.5)
ASBF left, au	322.2 (264.9 to 384.5)	249.9 (117.3 to 371.7)	183.0 (134.9 to 231.4)	229.3 (116.8 to 301.7)	-110.9 (-229.8 to -35.2)	-24.6 (-141.1 to 49.0)	28.0 (22.6 to 35.9)	60.9 (18.8 to 103.0)	-267.6 (-334.2 to -235.0)	-132.7 (-286.0 to -79.1) <sup>a</sup>
ASBF right, au	271.2 (227.9 to 355.0)	122.3 (90.9 to 320.5)	275.1 (217.9 to 343.4)	334.3 (133.0 to 413.5)	-19.2 (-101.6 to 23.2)	-18.5 (-82.0 to 258.9)	209.7 (188.6 to 260.6)	245.3 (104.1 to 419.9)	-39.0 (-112.8 to -0.4)	1.4 (-72.5 to 175.9)
TT, °C <sup>b</sup>	35.96 (35.88 to 36.08)	36.41 (36.05 to 36.54) <sup>c</sup>	36.21 (35.96 to 36.37)	36.35 (35.61 to 36.87)	0.14 (0.0 to 0.2)	-0.10 (-0.36 to 0.26)	36.11 (35.98 to 36.34)	36.02 (35.38 to 36.81)	0.08 (-0.02 to 0.22)	-0.22 (-0.96 to 0.27) <sup>c</sup>

To reduce the methodologic problem of multiple comparisons, statistical tests were only performed for the variables precooling and Δ cooling 2. au indicates arbitrary units.

<sup>a</sup>  $P \leq .01$  for differences between groups, using Wilcoxon-Mann-Whitney's test.

<sup>b</sup> Because of technical problems, TT was only measured in 45 control subjects and 13 patients with CFS.

<sup>c</sup>  $P \leq .05$  for differences between groups, using Wilcoxon-Mann-Whitney's test.

found in the CFS group, because skin AVAs are strongly controlled by sympathetic neural activity.<sup>22,34</sup>

Taken together, our baseline observations might indicate a general enhancement of sympathetic nerve activity to different regions and organs, including the forearm, the adrenals, and the heart. Patients' report of shivering, sweating, and paleness further suggest enhanced sympathetic outflow to skeletal muscles, sweat glands, and skin arterioles, respectively, a possibility that should be the subject of further research.

### Observations During and After Cooling

Strong, rapid cooling of 1 hand normally promotes a general enhancement of sympathetic nerve activity, causing increased plasma levels of both norepinephrine and epinephrine.<sup>7</sup> The stimuli for this response are not only reduced skin temperature in the immersed hand but also painful sensations. The similar increase in norepinephrine and epinephrine among control subjects and patients with CFS, as documented in this study, suggests that patients with CFS have preserved response abilities toward local cooling within the sympathetic nervous system. Thus, there are no indications of gross autonomic neuropathy, as have been proposed by others.<sup>35</sup> Although not the focus of this report, the significant reduction of normetanephrine and metanephrine on cooling observed in both groups is an interesting finding, which seems to be unique to this report.

Moderate, slow cooling of 1 hand normally causes a gradual reduction of ASBF down to a certain temperature level, at which ASBF suddenly ceases, presumably because of a coordinated closure of all of the AVAs<sup>23</sup> (Fig 1). Although the precise mechanisms behind this phenomenon have not been fully elucidated, one possible explanation is synthesis of local signal substances that increase the postsynaptic sensitivity for norepinephrine or antagonize neuronal reuptake.<sup>36,37</sup> Still, the closure is also dependent on central sympathetic outflow.<sup>23</sup> We have provided evidence of abnormally increased core body temperature at baseline among patients with CFS. If the part of the effector system that controls the AVAs functions normally, an adequate response would be to elicit heat loss, that is, ensuring preserved blood flow in the AVAs as the temperature in the water bath falls. Consequently, our observation of prolonged preservation of ASBF left in patients with CFS on cooling, which has not been reported before, might be interpreted as a normal regulatory response to abnormally increased core temperature at baseline. Accordingly, TT did fall in the CFS group during the experiment, indicating successful heat loss and normalization of core temperature, whereas the normal ASBF responses in the control subjects seemed to maintain TT constant in that group.

Alternatively, our results might indicate a defect in local vasoconstrictor mechanisms. Interestingly, recent experimental studies applying acetylcholine to small

skin areas have found stronger vasodilative responses among patients with CFS than healthy control subjects, suggesting subtle alteration of the endothelial microvascular regulatory system.<sup>38,39</sup> Other studies have documented a strong relation between CFS and the postural orthostatic tachycardia syndrome,<sup>40</sup> a condition that seems to be characterized by reduced norepinephrine reuptake in the sympathetic synapse.<sup>41</sup> Altogether, the previous studies and our own results underscore the need for research specifically addressing the complicated interaction of adrenergic, cholinergic, and other microvascular control mechanism in patients with CFS.

### Study Limitations

We instructed the participants to abstain from tobacco products and alcohol/caffeine-containing beverages before the experiments and also asked about alcohol/tobacco/narcotics in the questionnaire without finding any differences between the 2 groups. Still, we cannot completely rule out ingestion of illicit or nonillicit substances that might have influenced the results. Female reproductive hormones exert strong influence on sympathetic cardiovascular regulation<sup>42</sup>; thus, differences among the girls in the 2 groups with regard to sexual development and menstrual cycle might have introduced a bias. However, items addressing menstrual function in the questionnaire did not reveal any significant differences between the 2 groups.

Several symptoms reported by the patients with CFS are not specifically related to thermoregulatory disturbances but could be explained by, for instance, circulatory abnormalities, which indeed have been demonstrated in this group.<sup>2-4</sup> The neuroendocrine and cardiovascular responses to cooling were addressed in 2 separate experiments. A combined setup might have been more informative; in particular, measuring cardiovascular variables during strong cooling could have yielded better insight into the autonomic responses. Normetanephrine is the product of extraneuronal breakdown of catecholamines, whereas dihydroxyphenylethylene glycol mainly results from intraneuronal metabolism.<sup>7,29</sup> Concomitant measurement of this metabolite would have given more information on sympathetic nerve function. Between the 2 sets of experiments, the participants were allowed to eat, which might have altered skin blood flow. However, because the meals were standardized, this could hardly account for the observed differences between the 2 groups. In the moderate-cooling experiment, ASBF and TT were not measured before the acclimatization period; thus, the findings are not necessarily valid for ordinary ambient temperatures.

This study used a healthy control group, having a higher level of activity than the patient group. Thus, it is possible that our findings are a mere consequence of inactivity rather than of the underlying CFS pathophysiology. Additional research projects should consider us-

ing sedentary healthy control subjects or patients with other diseases having a comparable activity level to the patients with CFS. Finally, only 15 adolescent patients with CFS were studied, reducing the statistical power and bringing into question the generalizability of the results.

### CONCLUSIONS

Taken together, our results suggest that adolescent patients with CFS have abnormal catecholaminergic-dependent thermoregulatory responses both at rest and during local skin cooling. These results seem to support a hypothesis of sympathetic dysfunction in CFS.<sup>5,6</sup> Furthermore, they might explain important clinical symptoms.

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**Abnormal Thermoregulatory Responses in Adolescents With Chronic Fatigue Syndrome: Relation to Clinical Symptoms**

Vegard Bruun Wyller, Kristin Godang, Lars Mørkrid, Jerome Philip Saul, Erik Thaulow and Lars Walløe

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