

Does the Chronic Fatigue Syndrome Involve the Autonomic Nervous System?

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PURPOSE: To investigate the role of the autonomic nervous system in the symptoms of patients with chronic fatigue syndrome (CFS) and delineate the pathogenesis of the orthostatic intolerance and predisposition to neurally mediated syncope reported in this patient group.

PATIENTS AND METHODS: Twenty-three CFS patients and controls performed a battery of autonomic function tests. The CFS patients completed questionnaires pertaining to autonomic and CFS symptoms, their level of physical activity, and premorbid and coexisting psychiatric disorders. The relationship between autonomic test results, cardiovascular deconditioning, and psychiatric disorders was examined with multivariate statistics and the evidence that autonomic changes seen in CFS might be secondary to a postviral, idiopathic autonomic neuropathy was explored.

RESULTS: The CFS subjects had a significant increase in baseline ($P < 0.01$) and maximum heart rate (HR) on standing and tilting (both $P < 0.0001$). Tests of parasympathetic nervous system function (the expiratory inspiratory ratio, $P < 0.005$; maximum minus minimum HR difference, $P < 0.05$), were significantly less in the CFS group as were measures of sympathetic nervous system function (systolic blood pressure decrease with tilting, $P < 0.01$; diastolic blood pressure decrease with tilting, $P < 0.05$; and the systolic blood pressure decrease during phase II of a Valsalva maneuver, $P < 0.05$). Twenty-five percent of CFS subjects had a positive tilt table test. The physical activity index was a significant

predictor of autonomic test results (resting, sitting, standing, and tilted HR, $P < 0.05$ to $P < 0.009$); and the blood pressure decrease in phase II of the Valsalva maneuver, $P < 0.05$) whereas premorbid and coexisting psychiatric conditions were not. The onset of autonomic symptoms occurred within 4 weeks of a viral infection in 46% of patients—a temporal pattern that is consistent with a postviral, idiopathic autonomic neuropathy.

CONCLUSION: Patients with CFS show alterations in measures of sympathetic and parasympathetic nervous system function. These results, which provide the physiological basis for the orthostatic intolerance and other symptoms of autonomic function in this patient group, may be explained by cardiovascular deconditioning, a postviral idiopathic autonomic neuropathy, or both. *Am J Med.* 1997;102:357–364. © 1997 by Excerpta Medica, Inc.

The chronic fatigue syndrome (CFS) is characterized by disabling fatigue accompanied by postexertional malaise, musculoskeletal pains, headaches, sore throat, tender cervical or axillary lymph nodes, concentration difficulties, recent memory impairment, and sleep disturbance. A case definition for CFS was developed under the leadership of the U.S. Centers for Disease Control and Prevention (CDC) in 1988¹ and was revised in 1994.² The cause of the syndrome is unknown and there are no validated diagnostic tests.^{1–3}

There is some evidence suggesting autonomic nervous system involvement in the features of this syndrome.³ Autonomic signs and symptoms have appeared frequently in reports of sporadic and epidemic CFS, also called myalgic encephalomyelitis by previous investigators.^{4,5} Recent reports have suggested that a predisposition to neurocardiogenic syncope may underlie some of the symptoms of CFS,^{6,7} although it is not clear why patients with CFS develop such a predisposition. To explore the role of the autonomic nervous system in this syndrome and delineate the pathogenesis of this predisposition to neurocardiogenic syncope, we had a group of patients who fulfilled clinical criteria for CFS perform an extensive battery of autonomic function tests and complete questionnaires regarding their CFS symptoms, autonomic symptoms, and level of physical ac-

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tivity. In further distinction to previous studies of autonomic dysfunction in patients with CFS, we sought to determine whether two potential confounding factors often present in patients with CFS—physical deconditioning and associated psychiatric disorders—which might explain the autonomic dysfunction. In addition, we looked for evidence that the autonomic dysfunction seen in CFS might be secondary to a postviral, idiopathic autonomic neuropathy.

PATIENTS AND METHODS

Patients and Controls

The patients were recruited between 1993 and 1996 from the CFS Cooperative Research Center based at Brigham and Women's Hospital, Harvard Medical School. From a database of 383 subjects who were actively being followed for chronic fatigue, 261 met the original 1988 case definition for CFS.¹¹ Of these 261 patients, 146 (56%) endorsed symptoms referable to the autonomic nervous system based on their responses to a 76-item symptom questionnaire. The three criteria used to determine autonomic symptom eligibility were (1) dizziness upon standing and rapid heart beat; (2) dizziness upon standing and either nausea, diarrhea, constipation, or night sweats; and (3) rapid heart beat and either nausea, diarrhea, constipation, or night sweats. Patients had to meet one of the three criteria to be eligible. Recruitment letters were sent to the 104 eligible patients who live in New England as these were thought to be most likely to participate. Overall, 30 patients agreed to be tested, 26 patients in response to the recruitment letter and another 4 symptomatic, non-New Englanders who were recruited during a scheduled follow-up clinic visit. The remaining 78 patients who were sent recruitment letters either refused testing or did not respond. Age, gender, and illness duration were similar between the 30 participants and the 78 nonparticipants. Of the patients tested, results are presented here for 20 patients who could be age and sex matched to healthy controls recruited by advertisement. Three CFS subjects were tested and subsequently found to have specific diagnoses to account for their symptoms of fatigue. These subjects no longer satisfied the CDC case definition for the CFS and were eliminated. There was no difference in age, gender, illness duration, or test results between the 20 reported patients and the 10 patients tested but not included in this study. The controls were not selected for their level of fitness.

Autonomic Test Procedures

Medications affecting the autonomic nervous system were discontinued at least 48 hours before the

studies. All testing was carried out in the Autonomic Evaluation Unit of the Beth Israel Deaconess Medical Center. Subjects were instructed not to eat a large meal within the 2 hours preceding the study. Subjects were allowed sufficient time to acclimate to the testing environment and attain baseline autonomic function. Measurements of heart rate (HR) (Hewlett Packard EKG monitor 78203A; Andover, MA), blood pressure (BP) (Critikon Dinamap Vital Signs Monitor 1846SX/P, Johnson and Johnson; Critikon Inc., Tampa, FL), beat-to-beat BP (Finapres monitor; Ohmeda, Englewood, CO), and expiratory pressure (Validyne pressure transducer; Northridge, CA) were acquired and analyzed using a customized program.

The following autonomic tests were performed on all patients and control subjects: Heart rate variability with deep respiration (the maximum minus minimum heart rate difference [Max - Min] and expiratory to inspiratory ratio [E:I Ratio]); the BP and HR response to a 5-minute passive upright tilt on an electrically driven tilt table, active standing, and a Valsalva maneuver; the BP response to isometric exercise.⁸ A prolonged tilt table test of 45 minutes was performed on 16 CFS subjects. There was no insertion of intravenous lines or isoproterenol infusion. The tilt angle was 60 degrees.⁹⁻¹²

From the patients we obtained information about current and past nonpsychotic psychiatric conditions through use of the Diagnostic Interview Schedule (DIS).¹³ The DIS was administered so as to diagnose the presence of the following disorders, both before and after the onset of the CFS: major depression, dysthymia, and generalized anxiety disorder.

Twenty CFS patients completed a questionnaire in which they were asked about the temporal relationship (if any) between their symptoms of fatigue and a viral or flu-like illness and the temporal relationship (if any) between autonomic symptoms, and a viral or flu-like illness. All CFS patients completed an autonomic symptom questionnaire. Twenty CFS patients completed the College Alumni Health Study physical activity questionnaire.¹⁴⁻¹⁶

Statistical Methods

Comparisons between groups were made using Student's paired *t* test (two-sided). Results are expressed as mean \pm SEM. Relationships between variables were explored using stepwise multiple linear regression. $P < 0.05$ was considered significant.

RESULTS

Patient Demographics and Clinical Data

The mean age of the CFS subjects was 38.9 ± 2.1 years and controls 37.9 ± 1.8 years ($P = \text{NS}$). There were 14 women and 6 men.

The autonomic questionnaire measured the presence or absence of an autonomic symptom with a four-point ordinal scale where 0 denoted the subject never experienced the autonomic symptom and 3 denoted the subject frequently experienced the autonomic symptom. Patients endorsed the following symptoms on the questionnaire as occurring frequently: orthostatic lightheadedness (n = 10, 50%); intermittent nausea (n = 5, 25%); diarrhea (n = 2, 10%), constipation (n = 2, 10%), early satiety (n = 7, 35%), urinary frequency (n = 9, 45%), urinary urgency (n = 3, 15%), erectile difficulty in men (n = 2, 33.3%), excessive perspiration (n = 5, 25%), and cold extremities (n = 11, 55%). No control subjects reported that any autonomic symptom occurred frequently.

Seventeen of 19 CFS subjects reported that a viral infection preceded their chronic fatigue symptoms. Symptoms of fatigue began within 1 week of the viral infection in eight subjects (42%), within 2 weeks in one subject (5%), and within 1 month in two subjects (10%). Autonomic symptoms began within 1 week of the viral infection in three subjects (16%), within 2 weeks in two subjects (10%), and within 1 month in four subjects (20%).

Autonomic Test Results

Measures of baseline autonomic function are displayed in **Table I**. There were significant differences between the two groups in baseline heart rate in the supine ($P < 0.01$) and sitting ($P < 0.0001$) positions and the supine systolic blood pressure ($P < 0.05$). Tests of parasympathetic and sympathetic nervous system function are displayed in **Table II**. Tests of parasympathetic nervous system (the E-I ratio, $P = 0.001$; Max - Min, $P < 0.05$)—measures of heart rate variability with deep respiration—were significantly less in the CFS group. Measures of sympathetic nervous system function (systolic blood pressure [SBP] decrease with tilting, $P < 0.01$; diastolic blood pressure decrease with tilting, [DBP] $P < 0.05$; and the SBP decrease during phase II of the Valsalva maneuver, $P < 0.05$) were also significantly different in the CFS group. The Valsalva ratio was significantly higher in the CFS patients ($P < 0.05$). The maximum heart rate and increase in heart rate above baseline was significantly higher in the CFS group on standing ($P < 0.0001$ and $P < 0.05$) and tilting ($P < 0.0001$ and $P < 0.005$). Ten CFS subjects had an increase in heart rate of more than 30 beats/min when tilted to 60 degrees on the tilt table. Only one control subject had such an increase. Four CFS subjects had heart rate increases of ≥ 40 beats/min above baseline (see **Figure 1**).

Of the 16 CFS subjects who had a prolonged tilt table test, 4 subjects experienced syncope or devel-

TABLE I

Tests of Baseline Autonomic Function

	CFS	Controls
Supine systolic blood pressure	112.0 \pm 3.6*	104.4 \pm 1.75 [†]
Supine diastolic blood pressure	67.8 \pm 2.4	65.0 \pm 1.6
Supine heart rate	72.5 \pm 2.0	65.0 \pm 2.8 [†]
Sitting systolic blood pressure	116.4 \pm 4.5	108.6 \pm 1.9
Sitting diastolic blood pressure	69.3 \pm 2.1	70.4 \pm 2.1
Sitting heart rate	83.5 \pm 2.8	70.7 \pm 1.7 [§]

* Test results expressed as mean \pm SEM.

[†] $P < 0.01$; [‡] $P < 0.05$; [§] $P < 0.0001$.

CFS = Chronic fatigue syndrome.

TABLE II

Tests of Sympathetic and Parasympathetic Autonomic Function

	CFS	Controls
Expiratory:inspiratory ratio	1.24 \pm 0.03*	1.39 \pm 0.03 [§]
Maximum-minimum heart rate (beats/min)	22.1 \pm 1.8	28.4 \pm 2.2 [†]
Valsalva ratio	2.01 \pm 0.1	1.78 \pm 0.1 [†]
Isometric exercise (mm Hg)	7.7 \pm 1.4	8.5 \pm 1.7
Valsalva phase II systolic blood pressure fall (mm Hg)	-28.1 \pm 5.8	-5.8 \pm 5.7 [†]
Standing systolic blood pressure fall (mm Hg)	-2.8 \pm 2.3	-0.4 \pm 1.4
Standing diastolic blood pressure fall (mm Hg)	6.3 \pm 2.5	4.2 \pm 1.6
Standing maximum heart rate (beats/min)	97.9 \pm 3.0	79.8 \pm 2.1
Standing heart rate increase (beats/min)	22.6 \pm 2.6	14.5 \pm 1.8 [†]
Tilt table systolic blood pressure fall (mm Hg)	-14.7 \pm 2.2	-7.1 \pm 1.6 [†]
Tilt table diastolic blood pressure fall (mm Hg)	-2.0 \pm 2.4	2.4 \pm 1.6 [†]
Tilt table maximum heart rate (beats/min)	100.2 \pm 3.5	80.4 \pm 2.3
Tilt table heart rate increase (beats/min)	31.8 \pm 3.4	18.6 \pm 2.1 [§]

* Test results expressed as mean \pm SEM.

[†] $P < 0.05$; [‡] $P < 0.01$; [§] $P < 0.005$; ^{||} $P < 0.0001$.

CFS = Chronic fatigue syndrome.

oped symptoms of presyncope that were accompanied by a decrease in blood pressure requiring immediate premature test termination. The test was terminated in these subjects after 15, 26, 39, and 40 minutes on the tilt table. No controls experienced syncope or symptoms of presyncope. Five additional CFS subjects complained of orthostatic lightheadedness, but were able to complete the test.

Twenty CFS patients completed the College Alumni Health Study physical activity questionnaire. The index of physical activity derived from the College Alumni Health Study questionnaire in the CFS cohort was 925.7 ± 231.4 kcal/week.

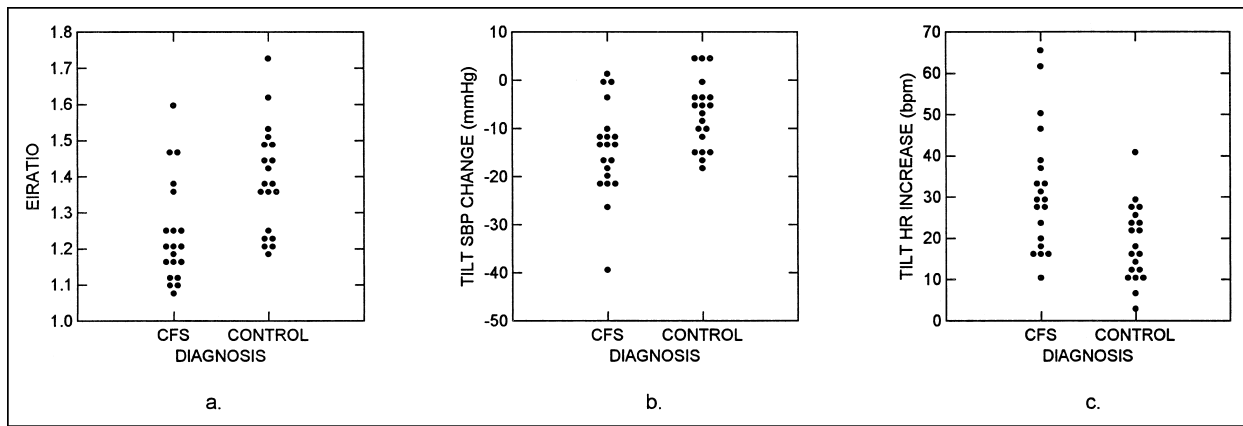


Figure 1. Autonomic test results in CFS patients and controls. (a) The expiratory inspiratory ratio (EIRATIO). (b) The blood pressure change in response to passive tilting. (c) The heart rate increase in response to passive tilting.

To determine the relationship between autonomic function and physical activity, depression, dysphoria, and anxiety before and after the development of the CFS, a linear regression model was created with the following format: $y = \beta_0 + \beta_1x_1 + \beta_2x_2 + \beta_3x_3 + \beta_4x_4 + \beta_5x_5 + \dots + \beta_ix_i$, where $\beta_0 =$ constant; $\beta_1 =$ the physical activity index, $\beta_2 =$ presence of major depression before CFS; $\beta_3 =$ presence of major depression after CFS, $\beta_4 =$ presence of generalized anxiety disorder before CFS; $\beta_5 =$ presence of generalized anxiety disorder after CFS, $\beta_6 =$ presence of dysthymia before CFS; $\beta_7 =$ presence of dysthymia after CFS. Only the physical activity index was a consistent significant predictor of the measure of autonomic function, predicting 45% of the variance in the resting HR ($P < 0.009$); 36% of the variance in the sitting HR ($P < 0.01$), 20% of the variance in standing HR ($P < 0.05$), 20% of the variance in HR on tilt ($P < 0.05$), and 56% of the variance in the SBP fall in phase II of the Valsalva maneuver ($P < 0.05$). The physical activity index, however, was not a significant predictor of the Max - Min, E:I Ratio, the SBP and DBP fall on tilting the other autonomic measures where the CFS patients differed significantly from the control group.

DISCUSSION

Previous case studies of the syndrome called myalgic encephalomyelitis, now thought to be the same illness as CFS, reported symptoms referable to the autonomic nervous system: orthostatic tachycardia, coldness of the extremities, hypothermia, episodes of sweating, profound pallor, sluggish pupillary responses, constipation, and frequency of micturition.^{4,5} Streeten and Anderson¹⁷ drew attention to the possibility that fatigue and exhaustion in some patients with the CFS might be attributable to failure to maintain blood pressure in the erect posture. More recent reports have documented a pre-

disposition to neurocardiogenic syncope in patients with symptoms of chronic fatigue, using the prolonged tilt table test,^{6,7} again suggesting autonomic dysfunction in the CFS. The cause and pathophysiologic basis of these changes in autonomic function remain unexplained.

Our study had three goals. First, we sought to define more precisely the pathophysiology of the autonomic nervous system abnormalities seen in patients with CFS, using a battery of tests of sympathetic and parasympathetic nervous system function, including but not limited to the prolonged tilt table test. Second, we sought to determine whether the autonomic test results were associated with, and thus might be explained by, two possible confounding factors: coexisting and premorbid psychiatric state, or cardiovascular deconditioning. Finally, we examined the evidence that the autonomic changes seen in the CFS might be secondary to a postviral, idiopathic autonomic neuropathy.

With regard to the study's first goal, several autonomic function test results were significantly different in the CFS group when compared to controls: measures of heart rate variability with deep respiration, the blood pressure decrease on tilting, the heart rate increase with postural change, the resting heart rate, and the blood pressure decrease in phase II of the Valsalva maneuver. Using a prolonged tilt test without isoproterenol to increase test specificity,¹⁸ we confirmed the predisposition of CFS patients to neurocardiogenic syncope as reported by others,^{6,7} although we found this to occur much less frequently. The differences observed in our testing localize to both the sympathetic and the parasympathetic divisions of the autonomic nervous system, and provide a pathophysiologic basis for the symptoms^{4,5} and tilt table abnormalities^{6,7} previously described. In contrast to Bou-Holaigah et al,⁷ who reported 96% of their CFS subjects and 29% of their

control subjects had an abnormal tilt table test result, only 25% of our CFS subjects had an abnormal test. This distinction may in part reflect different test techniques. The technique of Bou-Holaigah et al entails a 4-hour fast, intravenous line insertion, a tilt angle of 70 degrees, and the infusion of isoproterenol to provoke syncope, all of which increase the sensitivity but decrease the specificity of the tilt table test. Our test technique, which does not require a fast, intravenous insertion, or isoproterenol infusion, and has a tilt angle of 60 degrees, has greater specificity but lower sensitivity.¹⁸

With regard to our study's second goal of identifying confounding factors that might explain autonomic dysfunction, because there is a high prevalence of depression and anxiety in the CFS population, we postulated that some of the autonomic abnormalities might have reflected changes associated with an underlying psychiatric disorder. However, our study found that neither concurrent nor premorbid depression, anxiety, or dysthymia, correlated with any of the measures of autonomic dysfunction. Previous studies also have not found that depression is associated with reduced heart rate variability¹⁹ or clinically significant orthostatic intolerance.

On the other hand, we found some evidence that confounding from cardiovascular deconditioning could have explained some of the autonomic dysfunction we observed. The index of physical activity in the CFS patients was, as expected, significantly less than in a healthy representative population,²⁰ and the CFS patients, as reflected in their responses on the College Alumni Health Study physical activity questionnaire,¹⁴ very likely were deconditioned. Results derived from this widely used instrument correlate with physical activity diaries,¹⁵ maximal oxygen uptake,²¹ and physiologic parameters influenced by physical activity.²⁰

Previous studies have found that deconditioning eg, due to prolonged bed rest or to exposure to microgravity during space flight, result in orthostatic hypotension, an exaggerated tachycardia upon assuming the upright posture and reduced heart rate variability.²²⁻²⁵ In our study, the CFS patients experienced significant decreases in the SBP and DBP on tilt table testing but not on standing. They experienced an exaggerated tachycardia on both tilt testing and standing, and they had evidence of reduced heart rate variability as measured by the Max-Min and E:I Ratio. Thus, they had autonomic abnormalities that have been reported previously in deconditioned subjects.

At the same time, the physical activity score in our subjects did not correlate significantly with measures of heart rate variability, the SBP and DBP decrease on tilting. Thus, deconditioning alone did not fully explain these autonomic abnormalities.

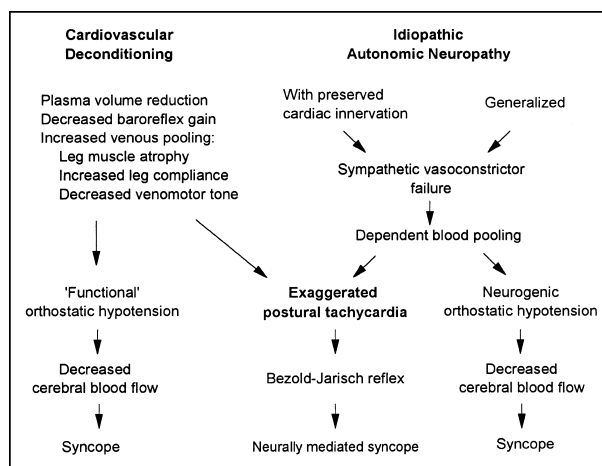


Figure 2. The relationship between cardiovascular deconditioning, autonomic neuropathy, the postural tachycardia syndrome, and orthostatic intolerance.

We also explored the possibility that, in addition to deconditioning, a postviral autonomic neuropathy—a common cause of sporadic autonomic dysfunction in previously healthy young individuals—might play a role in the autonomic test results. Eighty-nine percent of the patients in this study reported that the onset of fatigue was preceded by a flulike syndrome, a history typical of patients with CFS.² In 26%, the onset of autonomic symptoms occurred within 2 weeks and 20% within 1 month of the flulike syndrome—a time course consistent with a postviral, idiopathic autonomic neuropathy.²⁶⁻³² This disorder may present with sympathetic and parasympathetic deficits (pandysautonomia)²⁶⁻²⁸ or selectively involve the sympathetic or parasympathetic nervous system.³³⁻³⁵ The idiopathic autonomic neuropathy, like its motor counterpart the Guillain-Barre syndrome, is most likely immune mediated and is frequently associated with a previous infectious illness.^{30,31,36-38} The chronicity of the features of this autonomic neuropathy, which may have an acute or subacute presentation, is well documented.^{36,39} Although there is no identified specific cause of CFS, active and/or chronic infection with Epstein-Barr virus, human herpes virus type 6 (HHV-6), and enterovirus, among others has been associated with CFS.⁴⁰ Our results provide circumstantial evidence for an association between an idiopathic autonomic neuropathy and CFS. More definite proof of this association requires further study.

Therefore, it is possible that deconditioning and a postviral idiopathic autonomic neuropathy may contribute to the autonomic dysfunction in the CFS. On the basis of our results, in **Figure 2**, we present a model to explain the orthostatic intolerance observed in this patient group.

Orthostatic intolerance attributable to cardiovascular deconditioning is multifactorial. The pathophysiologic mechanisms include a reduction in plasma volume due to a compensatory natriuresis and diuresis in response to the redistribution of blood from the periphery to the central intravascular compartment that occurs during recumbency and other deconditioning states.^{22,41-43} Other factors are decreased responsiveness of the baroreflex to fluctuations in blood pressure^{23,24} and increased venous pooling due to disuse atrophy of the leg muscles,⁴⁴ increased leg compliance,⁴⁴ and loss of venomotor tone^{22,23} that results in decreased cardiac preload. These mechanisms result in *functional* orthostatic hypotension and a postural tachycardia on assuming the upright posture.

In contrast, *neurogenic* orthostatic hypotension due to an autonomic neuropathy is a consequence of deficient sympathetic nervous system-mediated vasoconstriction that leads to blood pooling in the dependent circulation and reduced cerebral perfusion on assuming the upright posture. Although patients with an autonomic neuropathy usually have an attenuated compensatory tachycardia, if, however, there is relative sparing of the cardiac autonomic innervation, this disorder may also be accompanied by an exaggerated postural tachycardia. The tachycardia, associated with both an autonomic neuropathy and deconditioning, particularly if accompanied by increased cardiac ionotropy, may result in the paroxysmal vasodepressor and bradycardic response characteristic of neurally mediated syncope by provoking the Bezold-Jarisch reflex.^{45,46} Thus, as summarized in Figure 2, orthostatic intolerance in the CFS subjects may not only have more than one etiology, but may also have at least two specific pathophysiologic mechanisms, namely, neurally mediated (vasovagal) syncope and orthostatic hypotension.

The CFS has features in common with another recently described syndrome characterized by orthostatic intolerance with an exaggerated postural tachycardia, variably called hyperadrenergic orthostatic hypotension,⁴⁷ sympathotonic orthostatic hypotension,⁴⁸ idiopathic hypovolemia,⁴⁹ and the postural orthostatic tachycardic syndrome.^{50,51} Symptoms in this patient group include lightheadedness, fatigue, palpitations, constipation, postprandial bloating, and vomiting. The syndrome is also frequently preceded by a viral infection.⁵⁰ In addition, the proposed pathophysiologic mechanisms for this syndrome also include a decrease in plasma or red cell volume leading to contraction of the intravascular space^{47,49,52,53} and a restricted autonomic neuropathy involving the lower extremities and depen-

dent regions but sparing the autonomic cardiac innervation.^{50,54} The relationship between this disorder and cardiovascular deconditioning and autonomic neuropathy is also displayed in Figure 2.

It is likely that orthostatic intolerance contributes to fatigue, the central symptom of CFS. Moreover, it may also lead to further inactivity that then compounds the symptoms of CFS. However, orthostatic intolerance is not likely to be the only factor and in many patients may not be the primary factor causing fatigue. Furthermore, some symptoms of CFS such as sore throats, myalgias, lymphadenopathy cannot be explained by autonomic dysfunction or orthostatic intolerance.

There are several limitations to our study. The overall study sample of patients seeking care in the CFS Cooperative Research Center may not be representative of the broader population of patients in the CFS community. Moreover, we deliberately selected patients with symptoms that could reflect autonomic dysfunction. Further study of unselected patients with CFS is warranted before these findings can be generalized to the entire CFS population. In addition, a larger subject number may have resulted in the emergence of one or more psychiatric factors as an additional predictor of autonomic test results.

Other central or peripheral nervous system pathologic processes may also be involved in producing the autonomic manifestations seen in the CFS. Reports of magnetic resonance imaging and single photon emission computed tomography abnormalities have implicated the central nervous system in the disease process of CFS⁵⁵⁻⁵⁷ and there is also preliminary evidence of pituitary-hypothalamic dysfunction.^{58,59} These possibilities were not addressed by our study.

There is at present no cure for CFS. The presence of autonomic dysfunction in CFS patients provides an important new potential avenue for improving those symptoms secondary to autonomic dysfunction. Volume repletion with increased sodium intake and treatment with agents such as fludrocortisone acetate and alpha-adrenergic agonists may benefit patients with orthostatic intolerance due to autonomic failure, deconditioning, and vasovagal syncope.⁶⁰ In addition, beta-adrenergic receptor blocking agents may benefit patients with vasovagal syncope.⁶¹ The results of our study also suggest that an exercise program may benefit the CFS patient. Such a program should be carefully tailored to the CFS patient, perhaps incorporating passive graded tilting on a tilt table for those patients who are unable to perform any exercise.⁶² These therapeutic options, alone and in

combination, cannot now be generally recommended for patients with CFS and should be the subject of a controlled study.

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