WILLIAM S. WILKE, MD
Department of Rheumatic and Immunologic Disease, Cleveland Clinic

FETNAT M. FOUAD-TARAZI, MD
Head, Hemodynamic and Neuroregulation Laboratory, Syncope Clinic, Imaging Section, Department of Cardiology, Cleveland Clinic

JOSEPH M. CASH, MD†
Chairman, Department of General Internal Medicine, Cleveland Clinic
†Dr. Cash died Feb. 16, 1998

LEONARD H. CALABRESE, DO
Vice chairman, Department of Rheumatic and Immunologic Disease, Cleveland Clinic

The connection between chronic fatigue syndrome and neurally mediated hypotension

ABSTRACT

Research from several groups of investigators indicates that some patients with chronic fatigue syndrome have abnormal vasovagal or vasodepressor responses to upright posture. If confirmed, these findings may explain some of the symptoms of chronic fatigue syndrome. There is also speculation that neurally mediated hypotension may be present in fibromyalgia. This article discusses the original research in this area, the results of follow-up studies, and the current approach to treating patients with chronic fatigue syndrome in whom neurally mediated hypotension is suspected.

KEY POINTS

The original research postulating a link between neurally mediated hypotension and chronic fatigue syndrome found that a high percentage of chronic fatigue patients had an abnormal response to the tilt-table test. Many of these patients responded to therapy.

Subsequent studies have been unable to replicate the findings of the original studies.

Use of tilt-table testing in patients with chronic fatigue syndrome is controversial; some physicians may wish to treat suspected cases of neurally mediated hypotension empirically.

IN 1995, RESEARCHERS at The Johns Hopkins University published two studies that postulated a relationship between neurally mediated hypotension and chronic fatigue syndrome,[1,2] generating considerable interest among patients and physicians alike.

In one of those studies,[2] the researchers found that 16 of 19 patients with chronic fatigue syndrome responded favorably to therapy for neurally mediated hypotension. Although those results were promising, the Hopkins researchers counseled caution because of the study's small sample size, short follow-up period, and lack of randomization, blinding, and placebo control.

Nonetheless, given the poor response of chronic fatigue patients to other therapies, these early results were met with great interest.

This article reviews the initial research proposing a link between chronic fatigue syndrome and neurally mediated hypotension, and discusses the possible physiological mechanisms involved. In addition, we will review subsequent research that attempted to replicate the Hopkins findings, and discuss a practical approach to diagnosing and treating neurally mediated hypotension when it is suspected in a patient with chronic fatigue syndrome.

PREVALENCE AND DEFINITION OF CHRONIC FATIGUE SYNDROME

Twenty-four percent of the population in the United States, at one time or another, experience fatigue lasting at least 2 weeks. Among 1,000 consecutive patients examined in an urban primary care center, 85 (8.5%) com-

plained of disabling fatigue lasting at least 6 weeks without apparent cause.[3] However, only 3 of 3,066 subjects met the formal criteria for chronic fatigue syndrome (as defined by the Centers for Disease Control and Prevention) in a carefully controlled cohort study of randomly chosen persons residing in the Pacific Northwest.[4]

The International Fatigue Study Group[5] suggests the following criteria for chronic fatigue syndrome to differentiate it from simple, intermittent fatigue:

Severe, debilitating fatigue lasting at least 6 months; and

Four or more of the following symptoms, present for at least 6 months.

- Impaired memory or concentration
- Sore throat
- Tender cervical or axillary lymph nodes
- Muscle pain
- Polyarthralgias
- New headache
- Unrefreshing sleep
- Postexertional malaise

Patients with fatigue of at least 1 month's duration who do not satisfy the criteria for chronic fatigue syndrome are said to have the syndrome of idiopathic chronic fatigue.

Is neurally mediated hypotension a cause of some chronic fatigue symptoms?

Chronic fatigue syndrome is not a new condition. In 1869, Beard[6] described patients with "nervous exhaustion" whose symptoms closely resembled those of chronic fatigue syndrome. Similar constellations of symptoms were recognized from the 1930s through the 1950s and given names such as Icelandic disease, Akureyri disease, royal free disease, epidemic vegetative neuritis, acute infectious myelitis, and benign myalgic encephalitis.[7] Bertrand Russell, the mathematician-philosopher, recognized the syndrome and commented on possible causes in an essay on fatigue in 1930: "The kind of fatigue that is most serious in the present day in advanced communities is nervous fatigue. This kind, oddly enough, is most pronounced among the well-to-do, and tends to be much less among wage earners than it is among business and brain workers."[8]

The etiology and pathophysiology of chronic fatigue syndrome are not well understood. Although immune abnormalities[9] and subtle inflammation[10] have been described, stress and neural hormonal dysfunction play a pivotal role.[11]

MECHANISM OF NEURALLY MEDIATED HYPOTENSION

Neurally mediated orthostatic hypotension has been proposed as a cause of some of the symptoms of chronic fatigue syndrome, among other hypotheses. The cardiovascular phenomena underlying this response have been reviewed previously.[12]

Low resting blood volume or excessive venous pooling during upright posture results in diminished return of blood to the heart. (Venous pooling is defined as a reduction in blood volume in the heart and lungs, which results from gravity causing the blood to pool in the veins below the heart.)

Reduced flow of blood back to the heart results in the "empty heart" phenomenon in the left ventricle and decreased cardiac output, which trigger increased sympathetic tone and release of the catecholamines epinephrine and norepinephrine. This in turn produces vigorous contraction of the left ventricle.

However, the vigorous systolic contraction of the ventricular wall around a ventricular cavity that has been reduced in size is thought to produce distortion and stimulation of C-fiber mechanoreceptors in the ventricular wall. These mechanoreceptors connect with afferent fibers of the vagus nerves. Their firing results in deactivation of the sympathetic nervous system and activation of the parasympathetic nervous system.

The clinical manifestation of this process is peripheral dilatation, termed "neurally-mediated hypotension," sometimes culminating in syncope. When accompanied by slowing of the heart rate, the syndrome is designated "vasovagal syncope."

TILT-TABLE TESTING

The tilt-table test allows study of cardiovascular responses to the effect of gravity on the venous circulation and cardiac preload. One testing protocol requires the patient to be supine for 5 minutes and then to be tilted to 70 degrees for 30 minutes or until an abnormal response occurs.

TABLE 1

Neurally-mediated hypotension in patients with chronic fatigue syndrome

INVESTIGATORS	YEAR	NO. OF SUBJECTS	RESPONSE		
			VASOVAGAL	VASODEPRESSOR	NONE
Bou-Holaigah et al[2]	1995	23	22 (96%)	0	1 (4%)
Lapp et al[13]	1996	71	17 (24%)	20 (28%)	34 (48%)
Freeman et al[14]	1997	20	4 (25%)*	NR†	NR†

*Vasovagal responses significantly higher than in age- and gender-matched controls
†NR = not reported

For patients who do not have an abnormal response after 30 minutes, a challenge with the beta-agonist isoprenaline is often performed.[12] Isoprenaline enhances adrenergic cardiac stimulation during the tilt test and shortens the time to precipitation of neurocardiogenic syncope. With isoprenaline, normal subjects experience a 10-mm Hg reduction of systolic blood pressure and a 5-mm Hg increase of diastolic blood pressure. The heart rate generally increases by 10 to 15 beats per minute, and the plasma norepinephrine level commonly doubles.

Abnormal responses include:

- Vasovagal reactions: a sudden decrease in blood pressure or a sudden decrease in heart rate after an initial increase, or both.
- Vasodepressor reactions, in which the blood pressure suddenly decreases and the heart rate increases.
- Progressive orthostatic hypotension, sometimes with an increase in the heart rate.
- Orthostatic tachycardia alone (an increase of > 30 beats per minute)
- Autonomic insufficiency with progressive orthostatic hypotension and no change in heart rate.
- Chronotropic insufficiency, in which the blood pressure responds normally but the heart rate is unchanged.

TILT-TABLE STUDIES IN CHRONIC FATIGUE SYNDROME

Rowe and colleagues at Johns Hopkins University[1] described seven consecutive nonsyncopal adolescents with chronic postexertional fatigue, who experienced significant hypotension during upright tilt-table testing. Four of these patients satisfied strict criteria for chronic fatigue syndrome. The same investigators subsequently described 23 adult patients with strictly defined chronic fatigue syndrome, 22 of whom experienced abnormal responses to upright tilt testing.[2] Only 4 of 14 control patients in this study experienced an abnormal response. The most consistent pattern in these studies was the vasovagal reaction.[1,2]

Patients with chronic fatigue syndrome did not differ from control subjects in their mean blood pressure before the test: 119/72 mm Hg in the chronic fatigue group, vs 118/75 in the control group. However, at termination, the mean blood pressure had decreased to 65/38 mm Hg in the chronic fatigue group, vs 118/66 in the control group ($P < .001$). Similarly, the mean heart rate at baseline was 75 in the chronic fatigue group and 68 in the control group; at termination, the mean heart rate was 77 in patients with chronic fatigue syndrome, vs 120 in the control group.[2]

The etiology of chronic fatigue syndrome is not well understood

Subsequent studies

The very high frequency of neurally-mediated hypotension initially reported in patients with chronic fatigue syndrome (22 of 23 subjects)[2] has not been independently corroborated in subsequent studies (TABLE 1).[13,14]

A series of 71 patients who satisfied strict criteria for chronic fatigue syndrome, demon-

strated a lower frequency of abnormal responses to upright tilt-table testing.[13] Only 17 (24%) of subjects demonstrated classic vasovagal response. Twenty (28%) other subjects experienced orthostatic tachycardia consistent with a vasodepressor response. In addition, a pattern of historical symptoms including nausea, diaphoresis, pallor, headache, and palpitations most consistent with volume depletion or excessive venous pooling was obtained.

In the most recent controlled series of 20 chronic fatigue syndrome patients selected for symptoms such as dizziness, tachycardia, and nausea,[14] only 4 (25%) demonstrated abnormal tilt-table responses consistent with neurally mediated hypotension. This low frequency of abnormal tilt-table responses is in contrast to the original Hopkins study.[2] Furthermore, in this series, physical deconditioning was a significant predictor of abnormal response, suggesting that it may be a major etiologic factor. Alternatively, the Hopkins group documented that the abnormal tilt-table response normalized with medical treatment before patients began an excercise program, which argued against deconditioning as a major factor responsible for the abnormal responses.[2]

Autonomic dysfunction has been reported in patients with fibromyalgia

Our group at the Cleveland Clinic explored the mechanisms underlying the abnormal response to tilt testing in 40 selected patients with chronic fatigue syndrome.[15] The protocol used radionuclide first-pass hemodynamic testing with ^{99M}Tc, measurement of blood volume by radioactive iodinated serum albumin scanning, and graded tilt testing at 15°, 30°, and 45° for 2 minutes each, followed by 60° tilt testing for up to 20 minutes. In this experience, venous pooling was a major mediator of progressive orthostatic hypotension, whereas hyperkinetic circulation or venous pooling were associated with orthostatic tachycardia.

Only 11 (28%) of the patients experienced progressive orthostatic hypotension, but most patients experienced some abnormal event, including neurocardiogenic responses in 10 patients (25%) and postural orthostatic tachycardia in 17 of patients (43%). This experience demonstrates that abnormal hemodynamic patterns are heterogeneous and common in chronic fatigue syndrome.

NEURALLY MEDIATED HYPOTENSION AND FIBROMYALGIA

Autonomic dysfunction has also been reported in patients with fibromyalgia. In those studies, fibromyalgia patients were found to have:

- Peripheral sympathetic dysfunction, characterized by increased cholinergic activity and decreased adrenergic activity.[16]
- Decreased vasoconstrictor responses to the cold pressor test.[17]
- Reduced heart rate response to exercise.[18]
- Abnormal tilt-table responses. In one series, seven (19%) of 37 patients with fibromyalgia had a positive tilt-table test, compared with two (9%) of 22 age-and-gender-matched controls.[19] In another report,[20] 12 of 20 patients with fibromyalgia experienced an increased heart rate and decreased blood pressures, vs none of 20 control patients.

The mechanisms underlying sympathetic dysfunction in fibromyalgia are not well understood. Given the near-identity of fibromyalgia and chronic fatigue syndrome,[21] it is not surprising that some patients with fibromyalgia experience abnormal neurally mediated blood pressure responses.

WHAT THESE FINDINGS MEAN FOR TREATING CHRONIC FATIGUE SYNDROME

In both chronic fatigue syndrome and fibromyalgia, response to treatment is often disappointing.[22] In these disorders, treatment is often considered successful if it produces an improvement in symptom severity of 25% to 30%.[23]

Therefore, the very positive treatment response demonstrated in the original report of neurally mediated hypotension in chronic fatigue syndrome has stimulated interest in tilt-table testing.[2] In this study, nine (47%) of 19 patients experienced nearly complete resolution of all symptoms after 2 weeks of volume expansion and other antisyncopal treatments, and an additional seven (37%) experienced at least some improvement. Further, when

responders were rechallenged with a repeat test, most demonstrated normal upright responses, which suggested that neurally mediated hypotension was associated with fatigue symptoms.[24]

In our experience and that of others, patients who have abnormal test results often give a history of syncope, light-headedness, diaphoresis, abdominal discomfort, blurred vision, and nausea associated with fatigue. Further, light-headedness is often exacerbated by physical exertion, a warm environment, a hot shower or prolonged standing.[2] However, studies to verify these impressions are lacking.

Should patients with chronic fatigue syndrome or fibromyalgia be referred for tilt-table testing? Some physicians may wish to document abnormal neurally mediated blood pressure responses by performing testing. Other physicians, however, may wish to treat empirically those patients who have suggestive symptoms. Roe et al[25] suggest a stepped approach:

- Increased intake of fluid (2 L/day) and salt (up to 3 g/day). If this does not relieve the symptoms, then add:
- Fludrocortisone 0.1 mg, beginning with 1/4 tablet per day and gradually increased to 1/2 tablet twice daily, plus a sustained-release potassium supplement. If these measures still do not relieve the symptoms, then substitute:
- Atenolol in an initial dose of 12.5 to 25 mg/day, or disopyramide gradually increased to 200 mg twice daily.
- Fludrocortisone should be avoided in patients with hypertension or fluid retention. As with all beta-blocking agents, atenolol should be avoided in patients with asthma or congestive heart failure.

Questions remain

There is little doubt that a subset of patients with chronic fatigue syndrome and fibromyalgia owe some of their symptoms to neurally mediated hypotension, but many questions remain.

- What is the frequency of neurally mediated hypotension among unselected populations of patients who fulfill criteria for chronic fatigue syndrome and fibromyalgia?
- What is the frequency of different patterns of neurally mediated hypotension in these patients?
- Are there historical symptoms which reliably identify subsets of patients with neurally mediated hypotension among chronic fatigue syndrome and fibromyalgia patients?
- Which treatments are best for each pattern of neurally mediated hypotension?
- What are the causes of neurally mediated hypotension? Increased circulating norepinephrine and epinephrine have been demonstrated in patients with depression[26]; might other underlying conditions predispose patients with chronic fatigue syndrome and fibromyalgia to this phenomenon?

As these questions are answered, a clearer role for tilt-table testing in chronic fatigue syndrome and fibromyalgia will emerge.

In chronic fatigue and fibromyalgia, response to treatment is often disappointing

REFERENCES

1. **Rowe PC, Bou-Holaigah I, Kan JS, Calkins H.** Is neurally mediated hypotension an unrecognized cause of chronic fatigue? Lancet 1995; 345:623–624.
2. **Bou-Holaigah I, Rowe PC, Kan J, Calkins H.** The relationship between neurally mediated hypotension and the chronic fatigue syndrome. JAMA 1995; 274:961–967.
3. **Bates DW, Schmitt W, Buchwald D, et al.** Prevalence of fatigue and chronic fatigue syndrome in a primary care practice. Arch Intern Med 1993; 153:2759–2765.
4. **Buchwald D, Umali P, Kith P, Pearlman T, Komaroff AL.** Chronic fatigue and the chronic fatigue syndrome: prevalence in a Pacific Northwest Healthcare System. Ann Intern Med 1995; 123:81–87.
5. **Fukuda K, Straus SE, et al. and the International Chronic Fatigue Syndrome Study Group.** The chronic fatigue syndrome: a comprehensive approach to its definition and study. Ann Intern Med 1995; 121:953–959.
6. **Beard G.** Neuroasthenia or nervous exhaustion. Boston Medical and Surgical Journal 1869; 3:217–220.
7. **Shafran SD.** The chronic fatigue syndrome. Am J Med 1991; 90:739–739.
8. **Russell B.** Chapter 5. Fatigue. In: The conquest of happiness. New York: Liveright, 1930:69.
9. **von Mikecz A, Konstantinov K, Buchwald DS, Gerace L, Tan EM.** High frequency of autoantibodies to insoluble cellular antigens in patients with chronic fatigue syndrome. Arthrit Rheum 1997; 40:295–305.
10. **Buchwald D, Wener MH, Pearlman T, Kit H.** Markers of inflammation and immune activation in chronic fatigue and chronic fatigue syndrome. J Rheumatol 1997; 24:372–376.
11. **Crawford LH, Demitrack MA.** Evidence that abnormalities of central neural hormonal systems are key to understanding fibromyalgia and chronic fatigue syndrome. Rheum Dis Clin North Am 1996; 22(2):267–284.
12. **Fouad-Terazi FM.** Using the tilt test to diagnose cause of

syncope. Cleve Clin J Med 1995; 62:339–341.
13. **Lapp CW, Glenn F, Davis P.** Neurally mediated hypotension and symptomatic orthostatic tachycardia in chronic fatigue syndrome (abstract). Proceedings of the American Association for Chronic Fatigue Syndrome Research Conference, 1996:23.
14. **Freeman R, Komaroff AL.** Does the chronic fatigue syndrome involve the autonomic nervous system? Am J Med 1997; 102:357–364.
15. **Chung J, Cash J, Calabrese L, Wilke W.** Mechanisms of abnormal response to head-up-tilt in chronic fatigue syndrome (abstract). PACE 1997; 20:1058.
16. **Qiao V-G, Vaeroy H, Morkrid L.** Electrodermal and microcirculatory activity in patients with fibromyalgia during baseline, acoustic stimulation and cold pressor test. J Rheumatol 1991; 18:1383–1389.
17. **Vaeroy H, Qiao V-G, Morkrid L, Forre O.** Altered sympathetic nervous system response in patients with fibromyalgia (fibrositis syndrome). J Rheumatol 1989; 16:1460–1465.
18. **van Denderen JC, Boersma JW, Zeinstra P, Hollander AT, van Neerbos BR.** Physiologic effects of exhaustive physical exercise in primary fibromyalgia syndrome (PFS): is PFS a disorder a disorder of neuroendocrine reactivity? Scand J Rheumatol 1992; 21:35–37.
19. **Clauw DJ, Radulovic D, Antonetti D, Bagati R, Baraniuk J, Barbey JT.** Tilt table testing in fibromyalgia (FM) [abstract]. Arthritis Rheum 1996; 39(suppl):S276.
20. **Bou-Holaigah I, Calkins H, Flynn JA, et al.** Provocation of hypotension and pain during upright tilt table testing in adults with fibromyalgia. Clin Exp Rheumatol 1997; 15:239–246.
21. **Goldenberg DL, Simms RW, Geiger A, Komaroff AL.** High frequency of fibromyalgia patients with chronic fatigue seen in a primary care practice. Arthritis Rheum 1990; 33:381–387.
22. **Wilson A, Hickie I, Lloyd A, Wakefield D.** The treatment of chronic fatigue syndrome: science and speculation. Am J Med 1994; 96:544–550.
23. **Jaeschke R, Adachi J, Guyatt G, Keller J, Wong B.** Clinical usefulness of amitriptyline in fibromyalgia: the results of 23 N-of-1 randomized controlled trials. J Rheumatol 1991; 18:447–451.
24. **Rowe PC, Bou-Holaigah I, Kan JS, Calkins H.** Improvement in symptoms of chronic fatigue syndrome is associated with reversal of neurally mediated hypotension [abstract]. Pediatr Res 1995; 37:338.
25. **Rowe PC, Bou-Holaigah I, Flynn J, Kan J, Calkins H.** Information for physicians. Neurally Mediated Hypotension Working Group (personal communication). Revised, October 1995.
26. **Gold BW, Goodwin FK, Chrousos GP.** Clinical and biochemical manifestations of depression: relation to the neurobiology of stress. N Engl J Med 1988; 319:384–353.

ADDRESS: *William S. Wilke, MD, Department of Rheumatic and Immunologic Diseases, A50, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.*

IN MEMORIAM

Joseph M. Cash, MD

In February, a good friend died suddenly. Joe Cash liked a challenge and it showed in the areas of rheumatology he embraced. He was drawn to difficult areas of clinical study, where the sum of what we know is outweighed by what remains to be discovered. He was fascinated by the use of biologic agents to treat connective tissue disease. And, of course, he confronted the controversial, such as chronic fatigue syndrome, fibromyalgia, and the clinical syndrome associated with silicone breast implants.

He had the courage to analyze existing information and take a stand. The buck stopped with Joe.

Unlike so many experts in scientific fields, Joe maintained a wide range of interests besides his work in academic rheumatology: sports, politics, religion, jazz, finance, and literature. He was learned about each. Conversations with Joe could be hard work, were always entertaining and were often an education.

We will miss him.

WILLIAM S. WILKE, MD