The Head-up Tilt Test in the Diagnosis and Management of Chronic Fatigue Syndrome

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Fatigue, as a symptom, refers to a sense of lethargy or loss of energy. Fatigue is common in infections, endocrine disorders, heart failure, chronic diseases of the lungs, liver or kidneys, malignancies, anemia, nutritional deficits, inflammatory arthritis, Parkinson's disease, depression, anxiety states, effect of certain medications, or drug withdrawal [1]. Population-based studies show that fatigue is one of the most common somatic symptoms, with as much as 20–30% of the population complaining of chronic fatigue [2]. Only a small fraction of these satisfy the clinical definition criteria for chronic fatigue syndrome [1].

Though CFS has received considerable attention it remains a controversial disorder. In 1988, the U.S. Centers for Disease Control published a "working case definition" of CFS [3]. The working case definition is an epidemiologic tool frequently employed when there are no diagnostic tests for a specific disorder [3]. The definition of CFS was revised by the CDC and an international study group in 1994. According to the new definition, CFS is clinically evaluated, medically unexplained fatigue present for at least 6 months duration; the fatigue is of new onset, not a result of ongoing exertion, not substantially alleviated by rest, and causing substantial reduction of previous levels of activity [4]. Other prominent features of the syndrome are chronic and recurrent low grade fever, pharyngitis, lymphadenopathy, arthralgia and neuropsychologic symptoms [Table 1]. Clinical practice guidelines for diagnosis and treatment of CFS were recently published by independent working groups [5–8].

The prevalence of CFS is 0.07–2% of the population [9], but the etiology and pathogenesis of CFS are poorly understood. The leading hypotheses put forward over the past decade include: a unique pattern of infection with an unrecognized pathogen, altered central nervous system function resulting from an abnormal immune response against a common antigen, a neuroendocrine disturbance, a neuropsychiatric disorder with clinical and neurobiological aspects suggesting a link to depressive disorders, or a psychologically determined response to infection or other stimuli occurring in "vulnerable" individuals [5,9]. The role of immune dysregulation in the pathogenesis of CFS was recently reviewed in the pages of this journal [10]. The heterogeneity within patient groups labeled as having CFS suggests that there are multiple factors contributing to this disorder [6]. A spectrum of different conditions might be included within the framework known as CFS.

Several studies have found a close connection between impairment of autonomic functions, i.e., dysautonomia, and CFS [5,9,11,12]. Abnormalities of the central nervous system on magnetic resonance imaging [13] and single photon emission tomography [14], as well as disruption of the hypothalamic-pituitary-adrenal axis and serotoninergic and noradrenergic pathways have been demonstrated [15,16], and a distal dysautonomia has been described in CFS patients [17]. Apart from its putative role in CFS pathogenesis, the significance of autonomic dysfunction in CFS can be addressed in terms of its value in diagnosis, monitoring the course and treatment of patients.

Diagnosis

The diagnosis of CFS rests largely on patient history, with no objective physical finding or laboratory test generally accepted or in common use to confirm the diagnosis. Moreover, all of the symptoms are non-specific and occur in many illnesses. According to the CDC definition criteria for CFS, the diagnosis is based on patient history and the exclusion of other diagnosable medical or

Table 1. Diagnostic criteria for chronic fatigue syndrome [4]

Fatigue

Clinically evaluated, unexplained, persistent or relapsing fatigue persistent for 6 months or more, that:

- is of new or definite onset
- is not the result of ongoing exertion
- is not substantially alleviated by rest
- results in substantial reduction in previous levels of occupational, educational, social or personal activities

And other symptoms

Four or more of the following symptoms that are concurrent, persistent for 6 months or more and did not predate the fatigue:

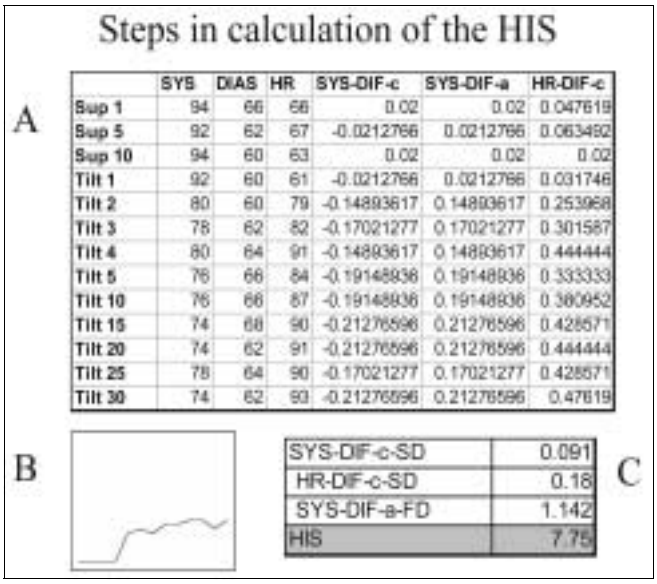
- impaired short term memory or concentration
- sore throat; tender cervical or axillary lymph nodes
- muscle pain; headaches of a new type, pattern, or severity
- unrefreshing sleep
- post-exertional malaise lasting more than 24 hours

CFS = chronic fatigue syndrome
CDC = Centers for Disease Control

psychiatric illnesses [4] [Table 1]. Two recent findings may advance the "objective" diagnosis of CFS. The first is a recent study showing that 72% of subjects in a group of patients with CFS had increased plasma levels of an abnormal 37 kDA protein [18]. The possible application of this finding for diagnostic purposes has not been assessed. The second development is the increasing evidence of dysautonomia as a possible marker of CFS.

The use of the head-up tilt test to assess autonomic function in CFS has been intensively investigated. The rapid response of blood pressure and heart rate to acute stimuli is under autonomic nervous control, and thus blood pressure and heart rate measurements during the HUTT can be used as one measure of cardiovascular autonomic activity, providing there is no evidence of organic heart disease, venous insufficiency or hypovolemia [19]. Recognized pathologic reactions to the HUTT are formally defined as vasodepressor and cardio-inhibitory reactions, orthostatic hypotension, the postural tachycardia syndrome and hyperventilation. In studies utilizing these outcome measures, evidence for abnormal cardiovascular reactivity was found in one-half of CFS patients [11,12,20]. These responses to tilt are non-specific, however, occurring also in a variety of disorders unrelated to CFS. Heart rate variability during the HUTT is another measure of abnormal cardiovascular reactivity in CFS. As with the classical outcome measures of the HUTT mentioned above, abnormalities of heart rate variability in CFS are not specific for this disorder and thus have no immediate practical application in the diagnosis of CFS [21]. A difficulty in assessing cardiovascular reactivity by the above-described classical methods arises from the high degree of non-linearity between external stimuli and cardiovascular response that characterizes autonomic cardiovascular modulation. A proposed approach for addressing this difficulty derives from the simultaneous quantification of blood pressure and heart rate fluctuations, in addition to the utilization of non-Euclidian mathematical analysis [22]. This approach was utilized in two refinements recently proposed for the assessment of cardiovascular reactivity – the Hemodynamic Instability Score and the Fractal and Recurrence Analysis-based Score.

The HIS involves computing blood pressure and heart rate changes during the course of the head-up tilt test, followed by processing the data curves yielded by image analysis techniques [23]. Blood pressure and heart rate are recorded during 10 minutes of recumbence and 30 minutes of head-up tilt. Thirty-one parameters of the heart rate and blood pressure were calculated. Multivariate analysis of these descriptors identified the best predictors for distinguishing the cardiovascular reactivity in CFS patients versus healthy controls. Using these predictors, an equation was deduced to compute the HIS [Figure 1]. Patients with CFS usually exhibited HIS values greater than -0.98. Reproducibility of the HIS with reference to the -0.98 threshold, on repeated HUTTs at 2–4 week intervals, was 100% [24]. However, a shortcoming of this method is that it can be applied only to patients who are able to complete 30 minutes of tilt, i.e, about 70% of patients. In the rest, the HUTT evokes syncope or near-syncope requiring interruption of the test [11,12,20].



	SYS	DIAS	HR	SYS-DIF-c	SYS-DIF-a	HR-DIF-c
Sup 1	94	66	66	0.02	0.02	0.047619
Sup 5	92	62	67	-0.0212766	0.0212766	0.063492
Sup 10	94	60	63	0.02	0.02	0.02
Tilt 1	92	60	61	-0.0212766	0.0212766	0.031746
Tilt 2	80	60	79	-0.14893617	0.14893617	0.253968
Tilt 3	78	62	82	-0.17021277	0.17021277	0.301587
Tilt 4	80	64	91	-0.14893617	0.14893617	0.444444
Tilt 5	76	66	84	-0.19148936	0.19148936	0.333333
Tilt 10	76	66	87	-0.19148936	0.19148936	0.380952
Tilt 15	74	68	90	-0.21276596	0.21276596	0.428571
Tilt 20	74	62	91	-0.21276596	0.21276596	0.444444
Tilt 25	78	64	90	-0.17021277	0.17021277	0.428571
Tilt 30	74	62	93	-0.21276596	0.21276596	0.47619

Figure 1. Processing the HIS. Systolic, diastolic blood pressure (BP) and heart rate (HR) values of patients with CFS, taken throughout the HUTT, are presented in Figure 1A. From the measured values, the relative changes of blood pressure and heart rate were calculated according to the equation: Blood pressure difference = $BP_{(n1....n13)}$ - BP_{n3} /BP_{n3}. Absolute values were then obtained by converting all results to positive numbers. Shown in the table are systolic BP differences as current (c) and absolute (a) values, as well as HR differences in current values (c). The BP and HR changes are used to calculate the SYS-DIFF-c-SD and HR-DIFF-c-SD [Figure 1C], which are independent predictors of the HIS. The third independent predictor of HIS is the SYS-DIFF-a-FD, and is processed from the time curve of the systolic BP differences [Figure 1B] by a fractal analysis program. Finally, the three independent predictors are applied to compute the HIS [Figure 1C]. In this specific case, HIS +7.75 is typical for CFS.

In an initial study, the HIS threshold of -0.98 differentiated CFS patients from healthy subjects, with 97% sensitivity (in patients who completed the full duration of the HUTT) and 96.6% specificity [23]. In subsequent studies, the specificity of the proposed HIS threshold of -0.98 for CFS was evaluated by comparing CFS patients to patients suffering from disorders with clinical similarity to CFS, as well as to disorders in which dysautonomia is known to be present [24,25]. The HIS threshold of -0.98 differentiated CFS patients (HIS = +2.02, SD 4.07) from healthy subjects (HIS = -2.48, SD 4.07) and from those with fibromyalgia, neurally mediated syncope, and non-CFS fatigue. The overall specificity of the HIS for the diagnosis of CFS was 84.5 and 85.1%, respectively [24,25].

To evaluate the applicability of the HUTT to the clinical situation, we reviewed our records of patients referred to us in the past 5 years, from 1 January 1998 to 31 December 2002. Eighty consecutive CFS patients, diagnosed according to the case definition criteria [4], underwent a tilt test that monitored blood pressure and heart rate, respiratory rate and the end-tidal pressure of CO_2 in the exhaled air. The HIS was then calculated. Five types of reactivity on the HUTT were distinguished: vasodepressor/cardio-inhibitory presyncope or syncope (leading to premature termination

HUTT = head-up tilt test
HIS = Hemodynamic Instability Score

of the HUTT), hyperventilatory (defined as end-tidal CO_2 ⩾25 mmHg), "CFS phenotypic" (defined as HIS <-0.98), mixed (CFS phenotypic reactivity associated with vasodepressor/cardio-inhibitory reactions not necessitating the discontinuation of the tilt), and normal. Approximately one-fifth of the individuals exhibited a normal response to the HUTT; another 30% of the CFS patients manifested classical non-specific endpoints of the test; 68.8% of patients demonstrated, via the HIS, cardiovascular reactivity typical for CFS [Table 2].

The finding that the HIS identified CFS patients from among others with dysautonomia suggests that there may be unique features to the CFS dysautonomia phenotype. To further support the prospect of defining a characteristic dysautonomia in CFS patients, an additional methodology was proposed to assess the cardiovascular reactivity during the HUTT. Beat-to-beat measurements of the heart rate and the pulse transit time were taken. Ten minutes recording with the patient supine was followed by recording 600 cardiac cycles on tilt, i.e., 5–10 minutes. Data were processed by recurrence plot and fractal analysis. Fifty-two variables were calculated for each subject. On multivariate analysis, the best predictors of CFS were determined and, based on these predictors, the Fractal and Recurrence Analysis-based Score was calculated [26]. The best cutoff differentiating CFS from a mixed control population was FRAS = +0.22. FRAS >+0.22 was associated with CFS (sensitivity 70% and specificity 88%). The possibility of distinguishing the cardiovascular reactivity of patients with CFS, with the aid of the HIS and FRAS, from reactivity in patients with other functional somatic syndromes, such as fibromyalgia [27] and neurally mediated syncope, as described above, suggests that a CFS-characteristic dysautonomia may be operative. In summary, four cross-sectional studies [23–26] converge to support the existence of a distinctive dysautonomia in CFS patients.

As a practical tool, the HUTT is easily administered; its use is not restricted by cultural constraints and it is applicable to a wide range of populations. There are many accessible and reasonably priced computer programs that can perform a fractal analysis and recurrence plot analysis. While performing a 10 minute supine to 30 minute tilt test is time consuming, the calculation of HIS is expeditious. The 10 minute supine to 10 minute tilt test to assess the FRAS is quick and well tolerated by CFS patients, but processing the data is time consuming. There are limitations to the applicability of the HIS and FRAS. Both methods were established and tested in patients with mild to moderate forms of CFS but have not been evaluated in subjects who are debilitated or bedridden. Second, results obtained in one laboratory have not yet been confirmed in other institutions. Third, pathologically elevated HIS and FRAS may theoretically occur, besides CFS, in cardiovascular deconditioning or under zero-gravity, in autonomic dysfunction associated with neurologic or chronic inflammatory disorders, or as a result of drug effects on the autonomic nervous system, though no systematic studies have assessed HIS and FRAS in any of these. The HIS is not helpful in sorting out the differential diagnosis between CFS and generalized anxiety disorder [23,24]. Fourth, as noted above, the distinctive dysautonomia phenotype is found in most but not all CFS patients.

The presence of a phenotypical dysautonomia in CFS may provide objective criteria for the diagnosis of CFS that, until now, could only be subjectively inferred. The difference between diagnosing CFS by CDC criteria alone or based on combined CDC and HIS or FRAS criteria is unclear, since there is no presently available test to definitely establish the diagnosis of CFS and serve as a gold standard. It may well be that a spectrum of different conditions might be included within the framework known as CFS [6].

FRAS = Fractal and Recurrence Analysis-based Score

Table 2. Outcome of the HUTT in 80 patients with CFS

Reactions on tilt	%
Vasodepressor/cardio-inhibitory presyncope or syncope*	18.8
Hyperventilatory**	3.7
Phenotypic (HIS >-0.98)	50
Mixed abnormal***	8.8
Normal	18.8

Blood pressure, heart rate and end-tidal pressure of CO_2 in the exhaled air were monitored.

* The tilt was prematurely terminated because of syncope, thus the HIS could not be computed.

** Hyperventilation was diagnosed when end-tidal pressure of CO_2 was ⩾ 25 mmHg.

*** Combination of the above abnormalities

Monitoring the course of fatigue

Severity of fatigue is the main parameter used to monitor the course of CFS. Patients' feeling of fatigue can be assessed with a self-administered fatigue questionnaire. Several such questionnaires are available. Some are restricted to mental and physical fatigue, such as the Chalder Fatigue Scale [28]. Other questionnaires provide multidimensional estimates, such as the Fatigue Severity Scale [29], the Profile and Fatigue-related Symptoms Scale [30], and a method that separately estimates mood, fatigue, symptoms, and disability [31]. There is no consensus as to whether multidimensional or unidimensional measures are preferable for assessment of fatigue-related symptoms [32].

To compare different methods that are used to assess fatigue-related symptoms, three groups of patients were evaluated in a cross-sectional study: CFS (n = 20), non-CFS fatigue (n = 20), and patients with familial Mediterranean fever serving as a control group (n = 25). Two questionnaires were employed, the unidimensional Chalder's Fatigue Severity Scale (11 items) and the multidimensional Fatigue Impact Scale (40 items). The patients were asked to quantify the extent to which fatigue affected them in relation to exemplar statements. The Chalder's modified questionnaire includes 11 items, each of them quantified on a scale of 0 to 3. Thus, the maximum Chalder's score is 33. In our institution, healthy subjects' fatigue scores ranged from 0 to 6. The Fatigue Impact Scale examines the patients' perception of functional limitations imposed by their fatigue over several months. Here too, the subjects rate the extent to which fatigue affected them in relation to exemplar statements. Each item is quantified on a scale

of 0 to 3: 0 = no problem to 3 = extreme problem. The Fatigue Impact Scale includes three subscales to assess perceived fatigue impact on cognitive functioning (10 items), physical functioning (10 items), and psychosocial functioning (20 items). The maximum score is 120. As may be expected from the selection of the groups, patients with fatigue as their main symptom (the CFS and non-CFS fatigue groups) had significantly higher Chalder's and Fatigue Impact scores than patients who did not complain of fatigue [Table 3]. We found that the fatigue severity as measured by Chalder's and Fatigue Impact scales was essentially similar. Correlations between Chalder's scores and Fatigue Impact cognitive scores were $r = 0.78$, $P < 0.0001$; between Chalder's scores and Fatigue Impact physical scores $r = 0.603$, $P < 0.0001$; Chalder's scores and Fatigue Impact social scores $r = 0.66$, $P < 0.0001$; and Chalder's scores and Fatigue Impact total scores $r = 0.74$, $P < 0.0001$. Hence, the simple Chalder's scale gave results comparable to the more complex and demanding Fatigue Impact Scale.

It would appear that an objective measure is needed to monitor the course of CFS. In particular, recognition of subtle changes, which may predict a clinical remission, would be important. The HUTT, with the calculated HIS derived from its performance, may be useful as such. A prospective study (Naschitz et al., personal communication) was performed to test the utility of the HUTT in monitoring the course of fatigue in CFS patients. Severity of fatigue was correlated with changes in dysautonomia, with fatigue questionnaires and tilt test performed sequentially and repeatedly during the course of the disease. In general, the HIS and fatigue severity correlated consistently in patients with CFS, but normalization of the HIS preceded remission of fatigue by an interval of 3–6 weeks. This study suggests that the HIS can serve as an objective means to monitor the course of CFS. Furthermore, the HIS may provide early information on the evolution of fatigue.

Treatment

In CSF patients, the disease disrupts and often devastates their personal and professional lives. A population surveillance study in the United States estimated that the cumulative 5 year recovery rate for CFS is 31% [33]. Many therapies have been suggested for CFS but none has proven successful [34,35]. Among the modalities tried are amantadine, doxycycline, acyclovir, immune serum globulin, dialyzable leukocyte extract, interferons, fluorocortisone, cimetidine, ranitidine, magnesium, primrose oil, vitamin B12, ampligen, essential fatty acids, liver extract, exclusive diets, and removal of dental fillings. A systematic review of 350 studies revealed that only two interventions have potential, namely cognitive behavior therapy and graded exercise [36]. However, both of these modalities are palliative at best.

Since dysautonomic cardiovascular reactivity is frequently present in CFS patients, it is possible that therapies directed at the autonomic nervous system may also alleviate fatigue symptoms. Midodrine HCl, a potent alpha-1-adrenergic agonist, is efficient in the treatment of hemodynamic disturbances such as symptomatic orthostatic hypotension, vasovagal syncope and postural tachycardia syndrome [37–40]. We hypothesized that midodrine treatment could benefit patients with chronic fatigue syndrome. We conducted a study on 10 CFS patients and 5 control patients with non-CFS fatigue; the patients had not taken medications for at least 2 weeks before entering the study. A dysautonomic reaction on the HUTT (i.e., HIS >-0.98) was present in all CFS but not in the non-CFS control patients. With midodrine treatment, 6 of the 10 CFS patients showed subjective and objective improvement that was maintained during 12 months of treatment. On the last HUTT the average HIS was -1.51 (range -0.87 to -1.98). Non-CFS fatigue patients, with normal HIS at baseline, showed no improvement on HIS and fatigue scores while taking midodrine (Naschitz et al., personal communication). Results of this pilot study may spur larger prospective studies on the principle of manipulating the autonomic nervous system to ameliorate both dysautonomic phenomena and fatigue in CFS.

Table 3. Fatigue scores in three patient groups, averages and standard deviations (in parentheses)

Variables	CFS (n=20)	Non-CFS fatigue (n=20)	Familial Mediterranean fever (n=25)	*P* value
Chalder's	18.0 (6.6)	17.5 (7.9)	5.5 (4.9)	<0.0001*
Fatigue Impact				
Cognitive	13.1 (7.5)	10.1 (7.5)	4.4 (6.6)	0.0019*
Physical	15.7 (10.5)	16.4 (7.5)	7.0 (5.2)	0.0002 *
Social	16.5 (10.9)	21.6 (13.9)	10.4 (9.1)	0.0096**

Significant differences were found between the following pairs: * CFS vs. FMF and non-CFS fatigue vs. FMF but not between CFS and non-CFS fatigue; ** non-CFS fatigue vs. FMF

Conclusions

The head-up tilt test reveals a particular dysautonomia in CFS patients that differs from dysautonomia in several other disorders. This distinct abnormality can be identified by HIS >-0.98 and FRAS >+0.22. Therefore, in the appropriate clinical context, the HIS and FRAS may be used to support the diagnosis of CFS that until now could only be subjectively inferred. A pilot study has suggested that midodrine treatment, directed at the autonomic nervous system in CFS, results first in correction of dysautonomia followed by alleviation of fatigue. This finding implies that dysautonomia is pivotal in the pathophysiology of CFS, at least in most of the patients, and that manipulating the autonomic nervous system may be effective in the treatment of CFS.

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