A Measure of Heart Rate Variability Is Sensitive to Orthostatic Challenge in Women with Chronic Fatigue Syndrome

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The use of symptoms generated by head up tilt (HUT) is not a useful tool in identifying chronic fatigue syndrome (CFS). We investigated whether heart rate variability (HRV) assessed early during HUT might be useful. A sample of 46 female subjects (24 with CFS and 22 sedentary, age-matched healthy controls; CON) who had exhibited no difference in time to syncope during tilt was examined for HRV responses to 10 min of 70° HUT after 5 min of baseline in the supine position. HRV data were analyzed by the method of coarse graining spectral analysis. Variables compared between groups included mean and standard deviation (SD_{RRI}) of RR intervals (RRI), amplitudes of low- (A_{LF}; 0.04–0.15 Hz) and high-frequency (A_{HF}; >0.15 Hz) harmonic as well as aperiodic, fractal (A_{FR}; $1/f^{\beta}$) spectral components, the spectral exponent β, and the difference in these values between baseline and HUT for each subject. In the supine baseline, only mean RRI was significantly ($P < 0.01$) lower in CFS than in CON. During HUT, however, mean RRI ($P < 0.01$), SD_{RRI} ($P < 0.01$), A_{HF} ($P < 0.05$), and A_{FR} ($P < 0.01$) were significantly lower in CFS than in CON. When the difference in values between baseline and HUT for each subject was examined, only the difference for A_{FR} (ΔA_{FR}) was significantly ($P < 0.01$) lower in CFS than in CON, suggesting that A_{FR} is a disease-specific response of HRV to HUT. When a cut-off level was set to $\Delta A_{FR} = -2.7$ msec, the sensitivity and the specificity in differentiating CFS from controls were 90% and 72%, respectively. The data suggest that a decrease in aperiodic fractal component of HRV in response to HUT can be used to differentiate patients with CFS from CON. Exp Biol Med 228:167–174, 2003

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Chronic fatigue syndrome (CFS) is characterized by medically unexplained fatigue of more than 6 months duration associated with a marked decrease in daily activity (1, 2). Despite extensive research, no definitive etiology for CFS has been discovered. A number of years ago, several groups of clinical researchers reported that patients with postural orthostatic tachycardia syndrome (POTS) or delayed orthostatic hypotension (DOH) frequently reported severe and chronic fatigue (3, 4). Subsequently, these disorders were found to co-exist in at least some patients with CFS (5, 6). The realization that patients with CFS had a cardiovascular system that responded abnormally to postural challenge led one group to do tilt testing in CFS and to report a very high rate of DOH in patients with CFS compared with controls (7, 8). Although subsequent studies have not confirmed this unique outcome after tilt testing in CFS (9, 10), data do exist to indicate that patients with CFS develop increased symptoms during orthostatic challenge (7).

Because other research focused on the pathogenesis of chronic orthostatic intolerance suggests the existence of autonomic dysfunction (11, 12), one major hypothesis to explain the symptom worsening seen in CFS after orthostatic challenge is autonomic dysfunction. However, data to support this hypothesis have not produced a clear result. Some workers report data showing autonomic abnormalities during postural challenge (13–16), whereas other do not (17, 18). Because some of these discrepancies might reflect differences due to inactivity in the patient group, we wanted to evaluate autonomic function in a carefully described and evaluated group of patients with CFS in comparison with sedentary group of healthy controls. Using head up tilt (HUT) as a probe, we investigated heart rate variability (HRV), reflecting cardiac autonomic responsiveness (19,

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20), and report a unique component of HRV that discriminates well between the two groups using an analysis that evaluates a test's sensitivity and specificity.

Materials and Methods

Study Design. The subjects with CFS (n = 39; 32 women and 7 men) were recruited from the larger pool available through the New Jersey CFS Cooperative Research Center. They met both the original (1) and revised (2) Center for Disease Control working case definitions as modified by our center to reduce patient heterogeneity, i.e., illness duration of less than 6 years, at least a 3 on 0–5 Likert scales of symptom severity in the month prior to recruitment, and no major psychiatric diagnosis in the 5 years prior to illness as assessed by a computerized diagnostic psychiatric interview (Q-DIS) (21) administered by trained personnel. Additional exclusion factors included loss of consciousness for more than 5 min and use of antihypertensives or benzodiazepines. Subjects taking any drugs with cardiovascular or orthostatic side-effects discontinued medication for at least three times the drug's half-life prior to testing.

Healthy control subjects (n = 31; 26 women and 5 men; CON) were recruited from the local community and were paid for their participation. These subjects were matched to CFS for age, gender, race, and education. The control subjects indicated that they did not work in an occupation requiring intense physical labor and were not participating in physical exercise for more than one session per week, i.e., they were sedentary. Control subjects were also excluded if they had any history of medical illness or major psychiatric diagnosis as determined by Q-DIS.

From this initial pool of subjects, we excluded men because of the relatively low number in our sample and the fact that gender can affect HRV-related variables used in the current study (22). Furthermore, to avoid bias caused by HRV analyses with shorter length of data, we only analyzed data containing at least 285 heartbeats, measured by a lead II electrocardiogram (21050A; Hewlett Packard, Palo Alto, CA). Consequently, the final number of subjects reported in the present study was 22 for CON and 24 for CFS. We confirmed that this selection procedure did not violate the age-matching between CON and CFS (see "Results" section). We also confirmed that patients with CFS and controls had similar rates of DOH. Thus, any autonomic changes found could be either important markers of the illness or a manifestation of an underlying pathological state.

The subjects reported to the laboratory at least 3 hr after their last meal. They abstained from any caffeine or alcohol ingestion after midnight and from performing strenuous exercise in the 24 hr prior to testing. All of the studies were conducted between the hours of 1300 hr and 1600 hr in a quiet, dimly lighted, and temperature-controlled laboratory. The subjects were not subjected to any kind of invasive instrumentation.

HUT was performed on a manual tilt table with foot support and straps to secure the subjects to the table. The subjects were asked to stand on the tilt table foot support while the tilt table was in a 70° position. To avoid an influence of even slight body movements on HRV-related variables (23), the subjects were instructed to restrain from moving their head or feet for the duration of the test. They remained in the supine position for 20 min, after which they were tilted in less than 4 sec to a 70° angle. The original HUT lasted for 45 min or until one of the following developed: syncope or presyncopal symptoms that were accompanied by a drop in systolic blood pressure of >25 mmHg with no concurrent increase in heart rate (7). In the present study, we analyzed data during the last 5 min of that baseline period as well as during Minutes 3–13 after subjects were rapidly transitioned to upright tilt. We chose this latter time to bypass transients related to postural change and because no subject exhibited orthostatic intolerance over this time period.

Data Analysis. We calculated the mean RR interval (RRI; msec) and standard deviation (SD_{RRI}; msec) of beat-to-beat RRI, sampled at 200 Hz, before being converted to the frequency domain. Before the analyses, the data were searched for extra or missing beats that could affect the results. Any artifactural RR intervals were corrected using summation or integer division. The HRV data were aligned sequentially to obtain equally spaced samples and the linear trend was eliminated by linear regression. The method of coarse graining spectral analysis (24) was used to break down the total power of HRV into regular periodic (or harmonic) components and aperiodic or fractal (FR) components. The harmonic components were further used to calculate the integrated powers in low-frequency (LF; 0.04–0.15 Hz) and high-frequency (HF; >0.15 Hz) regions (25).

The fractal component was plotted in a log-power versus log-frequency plane ($1/f^{\beta}$ plot), with the spectral exponent β estimated as the slope of the linear, least absolute deviation regression of the plot (26). Only the fractal power components within 20% difference from the total power were used for the regression (27). The value of β was used to measure the strength of the correlation (by greater β) of the fractal signals.

Statistical Analysis. The difference in age between CON and CFS was evaluated by one-way analysis of variance (ANOVA). The power values in LF and HF regions as well as the fractal power were square-root transformed to obtain the corresponding amplitudes (A_{LF}, A_{HF}, and A_{FR}, respectively; msec). The effects of HUT and illness were tested by two-way ANOVA for the main effects and the interaction, followed by one-way ANOVA for the effects of illness at baseline and during HUT separately. In addition, the difference in values between baseline and HUT for each subject was tested by one-way ANOVA to evaluate the interaction between subject group and physiological change after HUT, i.e., to determine if a disease-specific response to HUT existed. Furthermore, as the orthostatic sensitivity

in CFS has been reported to overlap with a clinical picture of POTS (28–30), we compared the results for patients with CFS with and without POTS, and non-POTS CON by two-way ANOVA for the main effects and the interaction and by one-way ANOVA with Duncan's multiple range test for values at baseline and during HUT and the differences in values between baseline and HUT. These differences were also tested between non-POTS CFS versus CON by one-way ANOVA to examine whether there was a disease-specific response to HUT in non-POTS CFS. POTS was diagnosed by an increase in heart rate of >30 beats/min or to >120 beats/min by HUT (3). These analyses were performed using SAS (SAS Institute, Cary, NC).

The ability of each variable to discriminate CFS from CON was evaluated by the technique of relative operating characteristic (ROC) (i.e., receiver or ROC) analysis (31, 32). The ROC curve is a graphical presentation of sensitivity versus specificity over a range of either increasing or decreasing cut off levels. The area under the ROC curve serves as a well-established index of diagnostic accuracy (32); a value of 0.5 arises from assignment to a class by pure chance, whereas the maximum value of 1.0 corresponds to perfect separation. In the present study, the ROC area was tested against a null hypothesis of $=0.5$ by using a gaussian approximation with a mean value of 0.5 and a variance of $(n + p + 1)/12np$, where n and p are the numbers in the negative (CON) and positive (CFS) classes, respectively. The analysis was run on variables at baseline, during HUT, and for the differences between baseline and HUT separately.

Results

HRV and the Spectra. Figure 1 shows the results for three representative subjects at baseline and during HUT. For a control subject (47-year-old female) in the supine position (Fig. 1A, left), RRI and HF spectral power were greater than those during HUT (Fig. 1A, right). Also, the greater HF power was associated with a respiratory-related harmonic (open minus filled bars) peak at around 0.3 Hz. However, the fractal power (filled bars) seemed to be increased by HUT, reflecting the presence of low-frequency transient changes in HRV.

In a 42-year-old patient (Fig. 1B), RRI was considerably lower both at baseline and during HUT as compared with the control subject in Figure 1A, and the spectral power was markedly diminished, as well. In addition to the decrease in the HF harmonic peak on going from baseline (Fig. 1B, left) to HUT (Fig. 1B, right), the fractal power was markedly diminished, resulting in almost flat and "monotonic" HRV. This patient with CFS also satisfied the criterion for POTS.

Another patient (40-year-old female) exhibited very different HRV dynamics (Fig. 1C) compared with the patient shown in Figure 1B. The mean RRI of this patient was almost comparable with that of the control subject in Figure 1A, indicating that this patient did not have POTS. Furthermore, the HF harmonic peak at baseline was even greater than that for the control subject. However, in contrast with the control subject, the aperiodic, fractal power was diminished, and HRV was simple and monotonic during HUT, similar to that exhibited by the patient in Fig. 1B.

Effects of Posture and Illness. There was no significant ($P > 0.05$) difference for age between CON (42.4 ± 7.7 yr; mean ± SD) and CFS (40.1 ± 9.6 year). There were significant main effects of posture in mean RRI ($P < 0.01$), SD_{RRI} ($P < 0.05$), A_{HF} ($P < 0.01$), and β ($P < 0.01$). Significant main effects of illness were found in mean RRI ($P < 0.01$), SD_{RRI} ($P < 0.01$), A_{HF} ($P < 0.01$), and A_{FR} ($P < 0.01$). Subsequent one-way comparisons revealed that only mean RRI was significantly ($P < 0.01$) lower in CFS than in CON in the supine baseline (Fig. 2A). However, during HUT, mean RRI ($P < 0.01$; Fig. 2A), SD_{RRI} ($P < 0.01$; Fig. 2B), A_{HF} ($P < 0.05$; Fig. 2D), and A_{FR} ($P < 0.01$; Fig. 2E) were significantly lower in CFS than in CON. Thus, in general, differences in the HRV-related variables between CON and CFS were more readily observed during HUT than at baseline.

When the difference in values between baseline and HUT for each subject was examined, only the difference for A_{FR} (ΔA_{FR}) was significantly ($P < 0.01$) lower in CFS than in CON (Fig. 2E), suggesting that a response of heart rate dynamics to HUT exists for patients with CFS and is reflected in A_{FR} (i.e., in "monotonic" HRV patterns). This was also confirmed by a significant ($P < 0.05$) interaction between posture and illness only for this variable. Inspection of Figure 2E shows that the patients (solid lines) have decreased A_{FR} in response to HUT when compared with CON (dotted lines), resulting in the smaller ΔA_{FR} during tilt.

ROC Analysis. The results of ROC analysis were generally compatible with those for the effects of illness above by one-way comparisons. That is, the ROC area was significantly greater than 0.5 in mean RRI at baseline ($P < 0.01$) and during HUT (Fig. 3A; $P < 0.01$), SD_{RRI} ($P < 0.01$), A_{HF} ($P < 0.05$), and A_{FR} (Fig. 3B; $P < 0.01$) during HUT, and ΔA_{FR} (Fig. 3C; $P < 0.05$).

However, the plots of sensitivity and specificity revealed differences in the diagnostic power among these variables. Although the sensitivity and specificity curves for ΔA_{FR} had a steeper cut off at a value of –2.7 msec (Fig. 3C), the curves for the other variables showed gradual decreases both in the sensitivity and specificity as cut off levels were varied (Fig. 3, A and B). When the cut off levels at which 90% sensitivity was obtained were calculated using a locally weighted regression technique (33), the corresponding specificity for ΔA_{FR} was greater than 10% (Fig. 3C). For mean RRI at baseline, SD_{RRI}, A_{HF}, and A_{FR} (Fig. 3B) during HUT, on the other hand, setting cut off levels to guarantee 90% sensitivity resulted in specificities as low as 50–60%. The only variable that had a diagnostic power approaching that for ΔA_{FR} was mean RRI during HUT

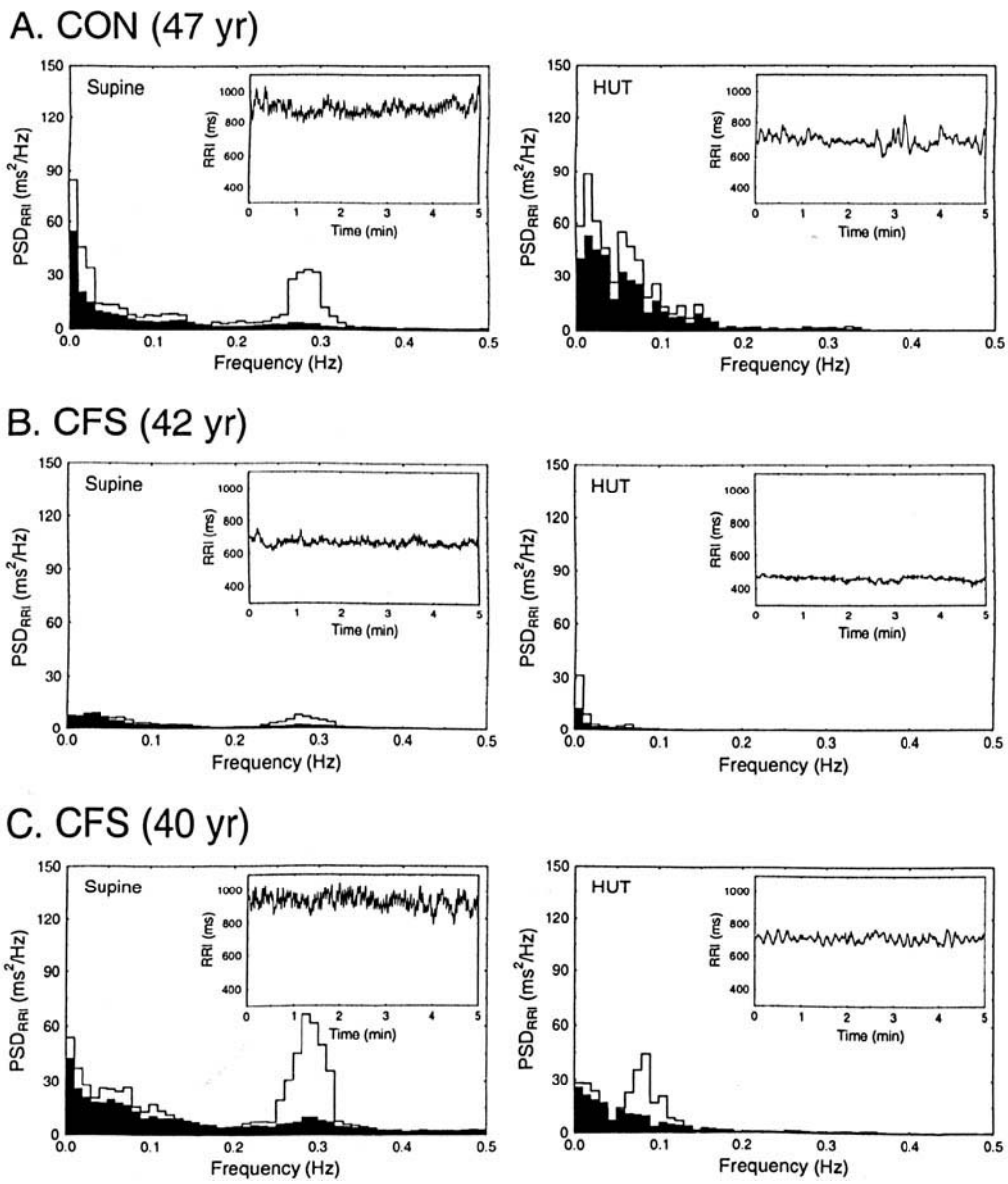

Figure 1. HRV (insets) and the harmonic and fractal spectra for three representative subjects at baseline (left) and during HUT (right). For the spectra, open bars represent the total (i.e., harmonic plus fractal) power spectral density, whereas filled bars the fractal power spectral density. The HRV data for the first 5 min of HUT are shown for comparisons with the data at baseline.

(Fig. 3A). However, ΔA_{FR} was more robust in terms of the trade off between sensitivity and specificity than the mean RRI during HUT (note that the distance between sensitivity and specificity curves was generally smaller in Fig. 3C than in Fig. 3A).

POTS. Of 24 patients with CFS, six patients also had POTS, whereas only one of 22 control subjects satisfied the criterion for POTS. The patients with POTS with CFS were significantly ($P < 0.05$) younger than non-POTS CFS and CON (Table I). When pooling POTS CFS, non-POTS CFS, and non-POTS CON together, there were significant main effects of illness in mean RRI ($P < 0.01$), SD_{RRI} ($P < 0.01$), A_{LF} ($P < 0.01$), A_{FR} ($P < 0.05$), and β ($P < 0.05$). The significant main effects of posture were observed in mean RRI ($P < 0.01$), SD_{RRI} ($P < 0.05$), A_{HF} ($P < 0.01$), and β ($P < 0.01$), Table I). The patients with POTS with CFS had significant ($P < 0.05$) decreases in A_{LF} and β during HUT as compared with the other groups (Table I). As expected by its definition, the POTS group had a significantly ($P < 0.05$) greater decrease in mean RRI in response to HUT. This was accompanied by significantly ($P < 0.05$) greater decreases in SD_{RRI} and A_{FR} (Table I).

The comparison between non-POTS CFS and CON revealed that only ΔA_{FR} was significantly ($P < 0.05$) smaller in non-POTS CFS than in CON. The other HRV variables were very similar between non-POTS CFS and CON (Table I). When the average $\Delta A_{FR} = -1.5$ msec for non-POTS CFS was used for a cut-off level (Fig. 3C), the sensitivity was still as high as 80%, with the specificity approaching 60%. For the other variables, the use of average values for

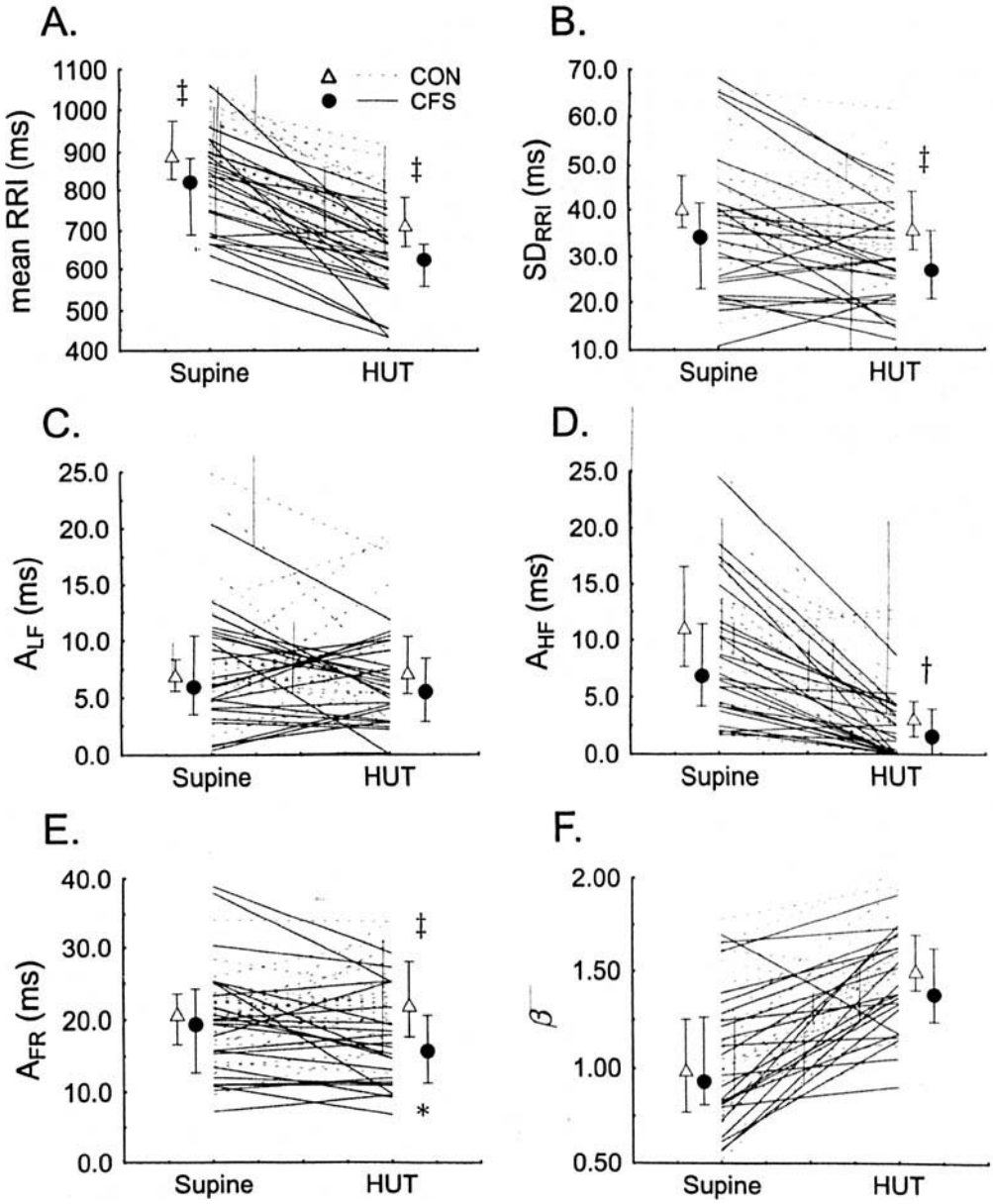

Figure 2. The effects of posture and illness on HRV-related variables. The response of each subject was shown either in a solid line for CFS or in a dotted line for CON. ● and △, the medians for CFS and CON, respectively. Vertical bars indicate interquatile ranges. † and ‡, $P < 0.05$ and $P < 0.01$ for differences between CFS and CON, respectively; *, $P < 0.01$ for a different response to HUT between groups.

non-POTS CFS resulted in marked decreases in the specificity values to 30%–40% (Fig. 3, A and B).

Discussion

To support the hypothesis of aberrant autonomic function during HUT, we should find evidence for autonomic dysfunction in patients with CFS compared with controls during postural challenge. Our results support this hypothesis in part, but not in a totally straightforward manner. Although patients with CFS did have lower mean RRI than controls, low values were seen both in the supine and head-up positions. Patients with CFS did have significantly lower SD_{RRI}, A_{HF}, and A_{FR} (see Fig. 2) than CON. However, of these variables, only the difference for A_{FR} (ΔA_{FR}, i.e., the fractal component of HRV) showed a significant interaction between posture and subject group. This important finding must be viewed in the context of previous studies showing altered HRV-related variables during HUT in CFS (14, 34, 35). None of these ever found an element of HRV that was sensitive to both diagnosis of CFS and orthostatic challenge. Although earlier work had suggested that the clinical response of patients with CFS to orthostatic challenge was quite different from that occurring in healthy controls, two recent well-controlled studies indicate that patients with CFS do not have increased rates of syncope or presyncope compared with controls (9, 10). Thus, finding a variable that clearly reflects the interaction between the existence of CFS and orthostatic challenge is important.

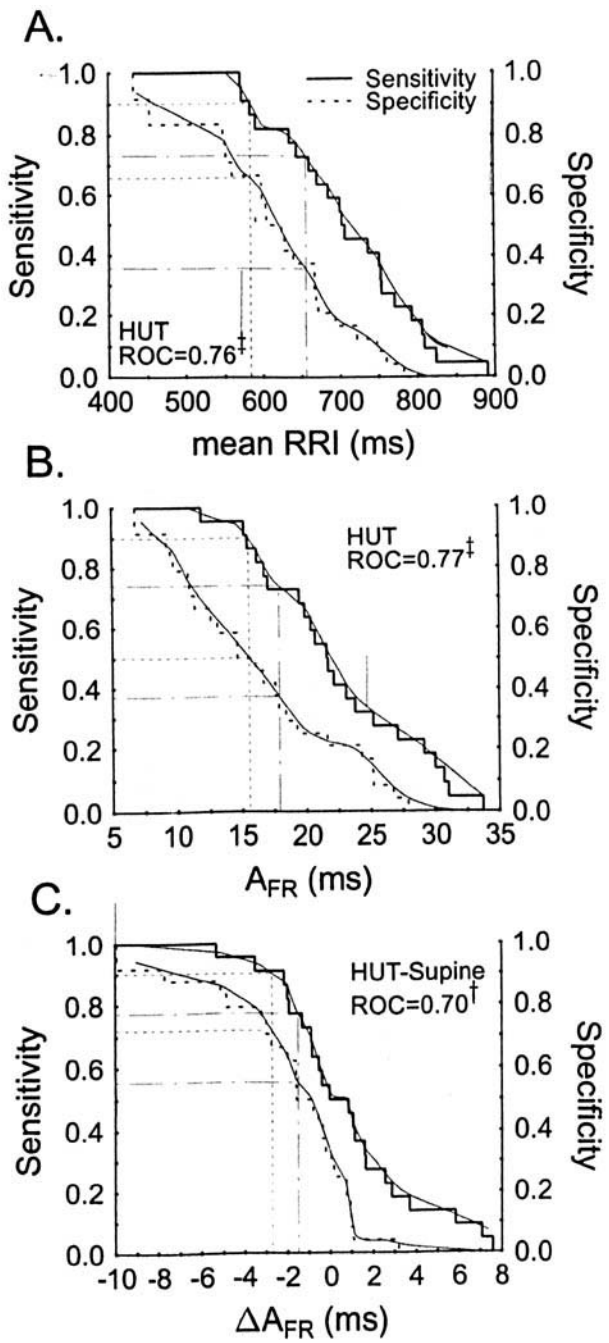

Figure 3. The plots of sensitivity (for positive CFS) versus specificity (for negative CON) for three variables during HUT. The individual sensitivity and specificity plots were smoothed by a locally (20% of the range of each variable) weighted regression (33), and the resultant curves (thin lines) were used to determine cut off levels and specificity values corresponding to 90% sensitivity (dotted lines). Broken lines show sensitivity and specificity values with cut off levels set to the average values for CFS without POTS.

The difficulty with this result is that the physiological significance of the amplitude of the fractal component of HRV remains unclear despite several years of intense study. The only recognized condition where this component of HRV is low (27) or the HRV loses its overall complexity (36) in healthy normals is during sleep; at this time, the input of higher brain centers to medullary cardiovascular areas is thought to be minimal. Furthermore, it was recently shown that this fractal component of HRV was not affected by minimizing behavioral factors such as body movements, postural transitions, and food intake, suggesting that it was intrinsic to the neurocardiac control system. However, this component of HRV was affected by pharmacological supression of the autonomic nervous system (37). Thus, we believe that complex and/or aperiodic changes in HRV, which were lost in the patients during HUT, may be related to central and/or intrinsic modulation of HRV. This interpretation suggests dysfunction of central neurocardiac control in CFS during HUT. However, how such a postulated central control mechanism would relate to peripheral autonomic function is not evident.

Recent reports have shown that the orthostatic sensitivity in CFS largely overlaps with a clinical picture of POTS (28–30), and we indeed could identify a subgroup of the patients with POTS. Our patients with POTS were younger than non-POTS CFS and CON, and the spectral exponent β, shown to be positively correlated with age (22), was also lower (Table I). In contradistinction to the age-related decrease in LF HRV that occurs in healthy normals (22), it was this younger subgroup of patients with CFS who showed a decrease in A_{LF} during HUT. Because the amplitude of vagally mediated, HF harmonic HRV was not altered in POTS (Table I), the decrease in LF harmonics might indicate a reduction in the amplitude of sympathetically mediated, vasomotor oscillation in HRV (19, 20). In addition, our finding a significant decrease in ΔA_{FR} in this group suggests the existence of an additional abnormality in intrinsic autonomic responsiveness (38).

Although the existence of POTS subgroup did affect the results of comparisons between CFS and CON, the selective decrease in A_{FR} in patients with CFS during HUT was not solely a function of a markedly smaller ΔA_{FR} in the POTS subgroup; we still found significantly smaller ΔA_{FR} in patients with CFS without POTS when compared with age-matched healthy controls (Table I). Our limited sample size of patients with POTS leaves open the question of what other physiological differences differentiate this group of severely fatigued patients from the larger non-POTS group. However, because the majority of our patients with CFS showed no obvious cardiovascular abnormality either in the resting condition or after HUT, we believe our finding a selective decrease in A_{FR} may be an important physiological manifestation of the non-POTS sensitivity of patients with CFS to orthostatic challenge.

We and others (9, 14, 28) have found resting heart rate to differentiate patients with CFS from controls. However, this is not a universal finding. Because so many variables can affect heart rate, it does not appear to be a useful measure in helping make the diagnosis of CFS. In contrast, ΔA_{FR} seems to be a useful discriminator. We evaluated the ability of ΔA_{FR} to differentiate between CFS and sedentary controls statistically. The test performed well, showing a sensitivity and specificity of 90% and 72%, respectively. The

Table I. The Effects of Posture, POTS, and CFS on HRV related variables

	POTS CFS ($n = 6$)	non-POTS CFS ($n = 18$)	non-POTS CON ($n = 21$)
Age‡ (year)	30.8 ± 8.9*	43.2 ± 7.8	43.1 ± 7.1
I‡ (msec)			
Supine	775 ± 184*	807 ± 93	898 ± 101
HUT¶	518 ± 91*	655 ± 73	727 ± 92
Difference	−256 ± 96*	−153 ± 54	−171 ± 58
SD_{RRI}‡ (msec)			
Supine	38.2 ± 20.3	35.0 ± 15.5	42.3 ± 11.1
HUT§	22.8 ± 13.2*	30.0 ± 8.2	38.3 ± 9.8
Difference	−15.5 ± 10.1*	−5.0 ± 10.1	−4.0 ± 10.6
A_{LF}‡ (msec)			
Supine	5.02 ± 5.41	7.56 ± 4.76	8.2 ± 6.48
HUT	2.08 ± 1.84*	7.07 ± 2.83	8.62 ± 5.26
Difference	−2.94 ± 4.97	−0.49 ± 4.31	−0.10 ± 7.32
A_{HF} (msec)			
Supine	9.23 ± 6.11	9.01 ± 7.53	11.8 ± 6.14
HUT¶	1.91 ± 1.82	2.21 ± 2.49	4.34 ± 3.44
Difference	−7.32 ± 5.02	−6.80 ± 6.20	−7.47 ± 6.15
A_{FR}† (msec)			
Supine	19.5 ± 9.4	19.3 ± 7.7	20.4 ± 5.7
HUT	12.8 ± 6.6*	17.8 ± 5.9	23.2 ± 6.3
Difference	−6.7 ± 5.2*	−1.5 ± 4.6**	2.7 ± 6.6
β†			
Supine	0.88 ± 0.43	1.08 ± 0.31	1.08 ± 0.36
HUT¶	1.21 ± 0.24*	1.49 ± 0.21	1.53 ± 0.26
Difference	0.33 ± 0.55	0.42 ± 0.26	0.45 ± 0.34

Note. Values are mean ± SD † and ‡, $P < 0.05$ and $P < 0.01$ for main effects of disease, respectively; § and ¶, $P < 0.05$ and $P < 0.01$ for the main effects of posture, respectively; *, $P < 0.05$ from the other groups; **, $P < 0.05$ from non-POTS CON.

ROC area for ΔA_{FR} was 0.70, which indicates the same test reliability as when physicians use the cardiac specific, MB isoenzyme of creatine kinase on admission to diagnose acute myocardial infarction (31). The data suggest that a simple HUT test for a brief, 10-min period without detailed physiological measures (e.g., blood pressure and sympathetic neural activity) can be a useful marker of CFS if a full range of HRV responses to HUT is evaluated in the frequency domain.

In the present study, we did not measure either blood pressure variability (39) or respiration (40)—both of which are known to affect HRV. However, we previously demonstrated that the fractal components of HRV behaved independently of blood pressure variability (41) and instantaneous lung volume (42). Thus, the main conclusion of the present study does not seem to be altered by this factor. Nevertheless, simultaneous observations of blood pressure and respiration would be needed in future research to elucidate more detailed autonomic cardiovascular controls in the patients with CFS (35).

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