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Use of time-frequency analysis to investigate temporal patterns of cardiac autonomic response during head-up tilt in chronic fatigue syndrome

Kazuhiro Yoshiuchi[a,b], Karen S. Quigley[c], Kyoko Ohashi[d], Yoshiharu Yamamoto[d], Benjamin H. Natelson[a,*]

[a] Department of Neurosciences, University of Medicine and Dentistry of New Jersey, New Jersey Medical School, 88 Ross Street, East Orange, NJ 07018, USA
[b] Department of Psychosomatic Medicine, Faculty of Medicine, The University of Tokyo, Japan
[c] Department of Psychiatry, University of Medicine and Dentistry of New Jersey, New Jersey Medical School, East Orange, NJ 07018, USA
[d] Educational Physiology Laboratory, Graduate School of Education, The University of Tokyo, Japan

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Abstract

Although a number of studies have reported alterations in cardiac autonomic nervous system function in chronic fatigue syndrome (CFS), the results are not consistent across studies. Reasons for these discrepancies include (1) the use of a heterogeneous patient sample that included those with orthostatic postural tachycardia (POTS), a condition with an autonomic changes, and (2) the use of frequency domain techniques which require a stationary signal and averaging data across relatively long epochs. To deal with these shortcomings, we used the smoothed pseudo-Wigner-Ville transform (SPWVT) to analyze heart rate variability (HRV) and blood pressure variability (BPV) during head-up tilt (HUT) by separating CFS patients into those with and without POTS. SPWVT has the advantage of providing instantaneous information about autonomic function under nonstable physiological conditions. We studied 18 CFS patients without POTS, eight CFS patients with POTS and 25 sedentary healthy controls during supine rest and during the first 10 min after HUT. While we found significant effects of postural change in both groups for all autonomic variables, there were significant group × time interactions between CFS without POTS and controls for only instant center frequency (ICF) within the low frequency region both from HRV ($p = 0.02$) and from BPV ($p = 0.01$). Although the physiological meaning of ICF still remains unknown, the data suggest that even CFS patients without POTS may have a subtle underlying disturbance in autonomic function.

Keywords: Chronic fatigue syndrome; Heart rate variability; Blood pressure variability; Time-frequency analysis; Smoothed pseudo-Wigner-Ville transform; Head-up tilt

Chronic fatigue syndrome (CFS) is a disabling disorder of unknown cause characterized by severe fatigue of more than 6 months duration. Because symptoms of orthostatic intolerance, such as disabling fatigue, dizziness, and diminished concentration, are often found in patients with CFS (Schondorf and Freeman, 1999), a number of studies have evaluated cardiac autonomic nervous system function during head-up tilt (HUT) in CFS patients compared to healthy controls. However, the results of previous studies have not been consistent. For example, De Becker et al. (1998) reported sympathetic dysfunction. Freeman and Komaroff (1997) showed alterations in both limbs of the autonomic nervous system. Finally, Yataco et al. (1997) did not find any difference in autonomic nervous system effects of HUT between CFS and controls.

One possible reason for the discrepant outcomes across studies is that the patients studied were never stratified based on whether or not they also had postural orthostatic tachycardia syndrome (POTS). It is known that 25–40% of CFS patients with orthostatic complaints also have POTS (Schondorf and Freeman, 1999), a syndrome associated with known autonomic nervous system dysfunction (Novak et al., 1996; Stewart, 2000). Therefore, failure to separate CFS patients with POTS from CFS patients without POTS could clearly lead to mixed results.

Another possible reason for the inconsistency among previous studies is that the principal method used to assess

* Corresponding author. Tel.: +1-973-676-1000x3578; fax: +1-973-395-7114.
E-mail address: bhn@njneuromed.org (B.H. Natelson).

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cardiac autonomic activity was the Fast Fourier Transform (FFT). Although FFT is an excellent technique for assessing heart rate variability (HRV) during steady states, it requires relative stationarity during the testing period, which makes it of limited value for changing conditions such as occur when subjects transition from supine to standing. Instead, different techniques are needed to evaluate autonomic function during the transition from lying to standing when relatively rapid autonomic nervous system changes occur (Jasson et al., 1997).

Recently, the smoothed pseudo-Wigner-Ville transform (SPWVT), an advanced spectral estimator based on the Wigner-Ville distribution, has been utilized for time-frequency signal analysis (Novak and Novak, 1993; Jasson et al., 1997). SPWVT has several advantages over FFT. It provides information about the variability in a signal such as heart period at very high temporal and frequency resolution; this allows the method to be used during periods of relative non-stationarity. In addition, SPWVT allows the assessment of instant center frequency (ICF), a weighted average of the spectrum (Jasson et al., 1997). ICF has been suggested to be a new global index of the relationship between sympathetic and vagal modulation (Jasson et al., 1997; Baillard et al., 2001). A measure like ICF that reflects relative shifts in sympathetic and parasympathetic activity is thought be particularly useful when the mode of autonomic control is known to be reciprocal as is true of HUT (Berntson et al., 1991).

Therefore, the aim of this study was to compare patterns of cardiac autonomic nervous system function of CFS patients before and immediately after HUT to that of controls using SPWVT specifically after separating CFS patients into those with and without POTS. This comparison is important because some studies have suggested that CFS patients showed abnormal responses to HUT, whereas we had failed to find this (LaManca et al., 1999). To examine whether this failure was due to the choice of measures or subjects, we re-analyzed data from this study using SPWVT.

1. Method

1.1. Subjects

From the pooled 26 CFS patients and 32 healthy controls, we excluded healthy subjects who were determined to have POTS if they had an increase in heart rate of >30 beats/min or exceeded 120 beats/min during HUT (Schondorf and Low, 1993). Then, the subjects in this study were three men and 15 women with CFS without POTS, two men and six women with CFS with POTS, and five men and 20 women who were in good health, did not exercise regularly and took no medications other than birth control pills. We have previously reported data on the orthostatic tolerance of these subjects (LaManca et al., 1999). The CFS subjects met both the original and revised Center for Disease Control working case definition (Holmes et al., 1988; Fukuda et al., 1994) as modified by our center to reduce patient heterogeneity (i.e., illness duration of less than 6 years and all symptoms reported as being at least "a substantial problem" in the month before recruitment). No subject in this study developed significant presyncopal symptoms or syncope during the 45 min HUT. All subjects signed informed consent, reviewed and approved by the UMDNJ New Jersey Medical School's Institutional Review Board.

1.2. Procedures

Subjects reported to the laboratory at least 3 h after their last meal. They abstained from any caffeine or alcohol after midnight and from performing strenuous exercise in the 24 h before testing. Smoking was not allowed prior to testing on the study day. HUT was performed on a manual tilt table with foot support and straps to secure the subjects to the table. They remained in the supine position for 20 min after which they were tilted to a 70° angle in less than 4 s. For specifics about the subjects and the procedures, see our earlier report (LaManca et al., 1999). RR interval (RRI) and systolic blood pressure data were analyzed during a 5-min baseline period just before head-up tilt when subjects rested supine and during a 10-min period just after subjects were tilted to the 70° position.

1.3. Data analysis

ECG was recorded from a lead II. Arterial blood pressure was recorded continuously with Finapres (Model 2300, Ohmeda, Louisville). The Finapres cuff was placed on the subject's left index finger and kept at approximately heart level in an adjustable arm support. ECG and blood pressure data were digitized at 200 Hz. Data were analyzed off-line using a program implemented in S-plus (Statistical Sciences, Seatle, WA) to obtain beat-to-beat RRIs and systolic blood pressure (SBP) for off-line analysis. The RRI and SBP data were reviewed for errors in the detection process and corrected manually.

The RRI and SBP data were resampled equidistantly at 2 Hz and the d/c component was eliminated using LOWESS, a robust locally weighted regression (Cleaveland, 1979). HRV and blood pressure variability (BPV) were analyzed with a time-frequency analysis method, the SPWVT (Novak and Novak, 1993; Jasson et al., 1997), which is a method that leads to reduction of cross-terms or spectral interference (see Appendix A). A Gaussian window (length of 128 samples, width alpha 2.5) was used as a frequency smoothing window and a rectangular window (length = 64 s) was used as a time smoothing window. A spectrum was obtained every 0.5 s (2 Hz), and contained an array of 128 power values corresponding to 128 equally spaced frequencies with a window length of 64 s (Jasson et al., 1997; Baillard et al., 2001). The power of each spectrum in ms^2 was calculated for high (HF, 0.15–0.40 Hz) and low frequencies (LF, 0.04–0.15 Hz) (Task Force, 1996). LF/HF in HRV was also calculated. Data for ICF, which represents a weighted average of the spectrum were

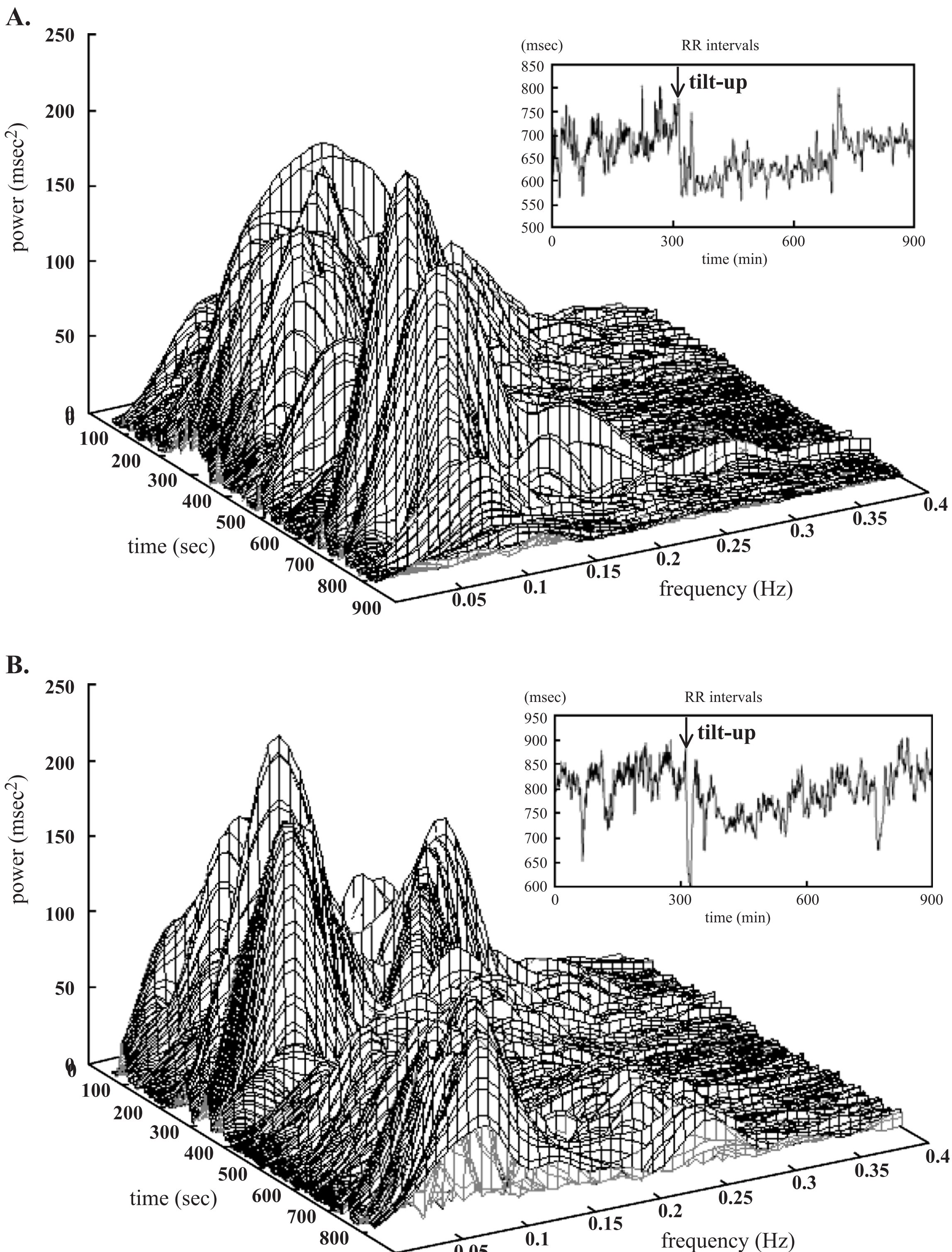

Fig. 1. Typical 3D representation of instantaneous time-frequency analysis of RR intervals using the smoothed pseudo-Wigner-Ville transform during baseline and head-up tilt in a patient with chronic fatigue syndrome without postural orthostatic tachycardia syndrome (A) and a healthy subject (B) with graphs of corresponding RR intervals.

calculated for the LF region according to the following formula:

$$\mathrm{ICF} = \frac{\sum_{k=0.04}^{0.15} kp(k)}{\sum_{k=0.04}^{0.15} p(k)}$$

where $p(k)$ is the power spectrum derived by SPWVT. Then, consecutive spectral powers and ICFs were averaged over 1-min intervals to evaluate the temporal profile during rest and tilt. In addition, the local maximum power in LF and HF, which is defined as the maximum spectral power for each 1-min sample within LF and HF respectively, was also calculated (Novak et al., 1999). The total number of averaged data points for each variable was 13 because of the window length of 64 s.

1.4. Statistical analysis

The dependent variables derived via SPWVT, RR intervals and SBP were evaluated using ANOVA for repeated measures (3 Groups × 15 Time Periods for RR intervals and

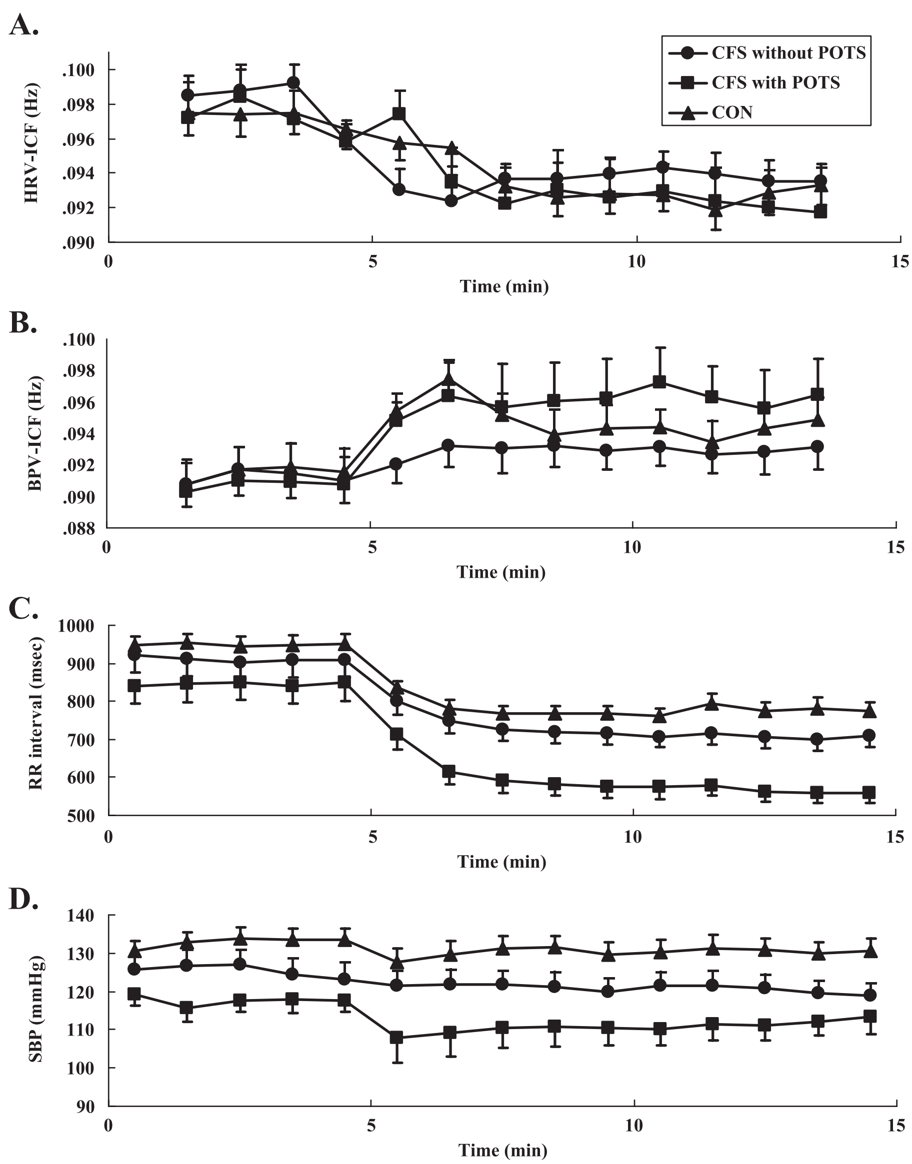

Fig. 2. Group averages of instant center frequencies (ICFs) in LF calculated from heart rate variability (HRV) and blood pressure variability (BPV) using the smoothed pseudo-Wigner-Ville transform (SPWVT), RR intervals and systolic blood pressure during baseline and head-up tilt in chronic fatigue syndrome (CFS) patients without postural orthostatic tachycardia syndrome (POTS) (closed circles), CFS patients with POTS (closed squares) and healthy control subjects (closed triangles). Significant main effects of time were seen in all variables, significant main effects of groups were seen in RR intervals (CFS with POTS < CON, $p=0.004$) and SBP (CON < CFS with POTS, $p=0.006$), and significant interactions of Group × Time were seen in HRV-ICF, BPV-ICF and RR intervals ($p=0.024$, $p=0.01$ and $p<0.001$, respectively). Error bars shows S.E.M. of each variable. CON, controls; HRV-ICF, instant center frequency calculated from HRV using SPWVT; BPV-ICF, instant center frequency calculated from BPV using SPWVT.

SBP and 3 Groups × 13 Time Periods for the variables derived via SPWVT) and Bonferroni's multiple comparison test. In addition, Pearson correlation coefficients between ICF calculated from HRV using SPWVT and RR intervals and between ICF calculated from BPV using SPWVT and SBP were calculated to investigate the physiological meanings of the ICFs. A p value of <0.05 was considered significant.

2. Results

2.1. Subject characteristics

There were no significant differences either in age (36.6 ± 7.1, 38.3 ± 11.3, and 40.4 ± 7.4 for CFS without POTS and with POTS, and controls, mean ± SD, respectively) or gender between CFS patients and controls.

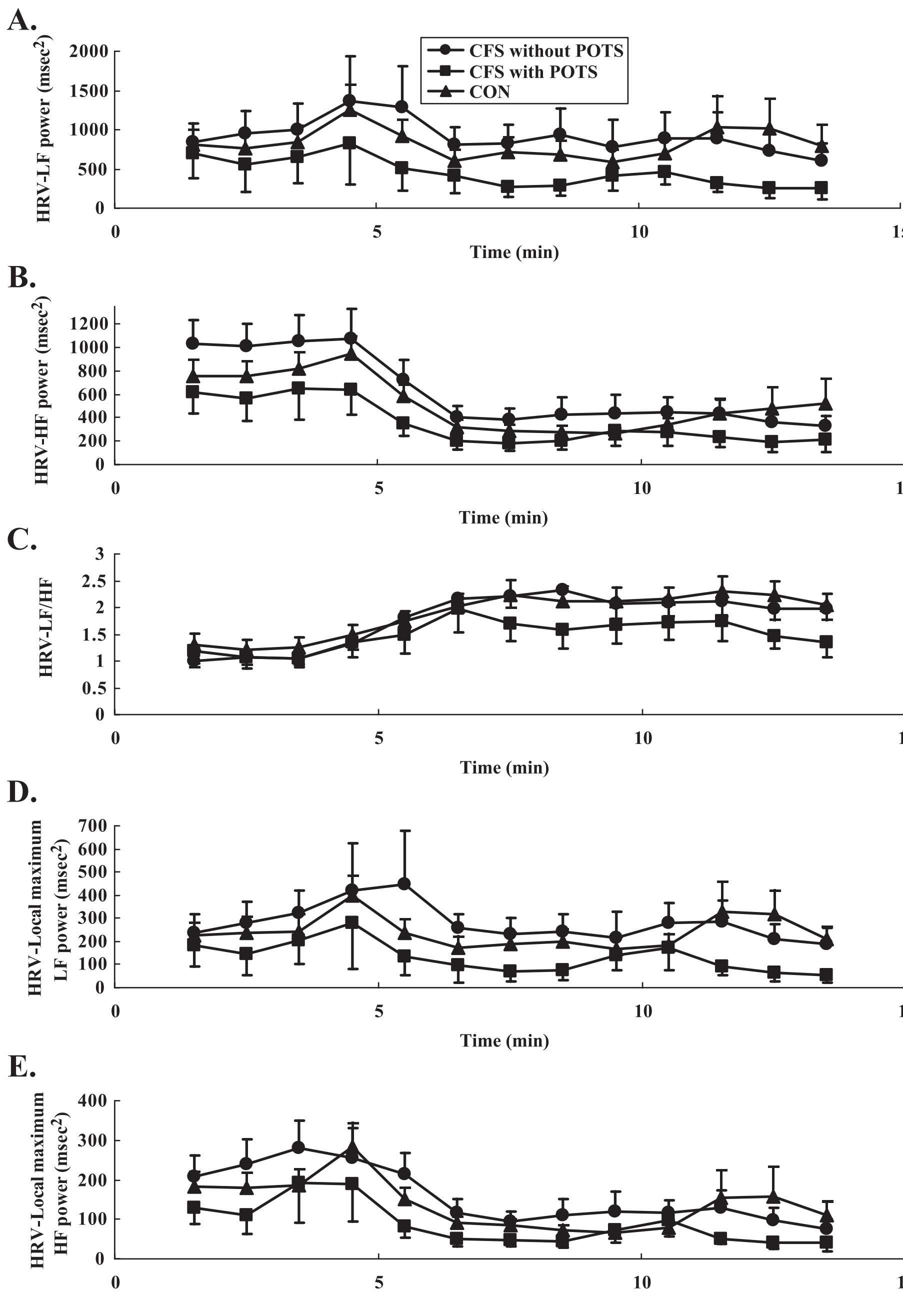

Fig. 3. Group averages of LF (A) and HF (B) power, LF/HF (C), and local maximum power in LF (D) and in HF (E) calculated from heart rate variability (HRV) using the smoothed pseudo-Wigner-Ville transform (SPWVT) during baseline and head-up tilt in chronic fatigue syndrome (CFS) without postural orthostatic tachycardia syndrome (POTS) (closed circles), CFS patients with POTS (closed squares) and healthy control subjects (closed triangles). There was a significant main effect of time for each variable. Error bars shows S.E.M. of each variable. CON, controls; HRV-LF power, LF power calculated from HRV; HRV-HF, HF power calculated from HRV; HRV-LF/HF, LF/HF calculated from HRV; HRV-local maximum LF power, local maximum power in LF calculated from HRV; HRV-local maximum HF power, local maximum power in HF calculated from HRV.

2.2. Temporal patterns in cardiac autonomic function

2.2.1. Heart rate variability

Fig. 1 shows a typical 3D representation of instantaneous time-frequency analysis of RR intervals with SPWVT during baseline and HUT in a patient with chronic fatigue syndrome (A) and a healthy subject (B).

There were significant main effects of time for all variables (Figs. 2 and 3), RRI ($p<0.001$), LF ($p<0.001$) and HF ($p<0.001$) power, LF/HF ($p<0.001$), ICF in LF ($p<0.001$), and local maximum power in LF ($p<0.001$) and in HF ($p<0.001$) (Fig. 3).

There were significant interactions of group x time for ICF within LF and RR intervals ($p=0.024$ and $p<0.001$, respectively, Fig. 2A and C). This result means that the temporal patterns of ICF of CFS patients without POTS differs from that of controls, and the patterns of RR intervals of CFS patients with POTS differs from that of controls. The latter result was expected due to the definition of POTS. There was also a significant group main effect for RR intervals ($p=0.004$, Fig. 2), which showed that heart rate in CFS patients with POTS was significantly higher than in controls.

2.2.2. Blood pressure variability

There were significant main effects of time for SBP ($p<0.001$), LF ($p<0.001$) and HF ($p<0.001$) power, ICF in LF ($p<0.001$), and local maximum power in LF

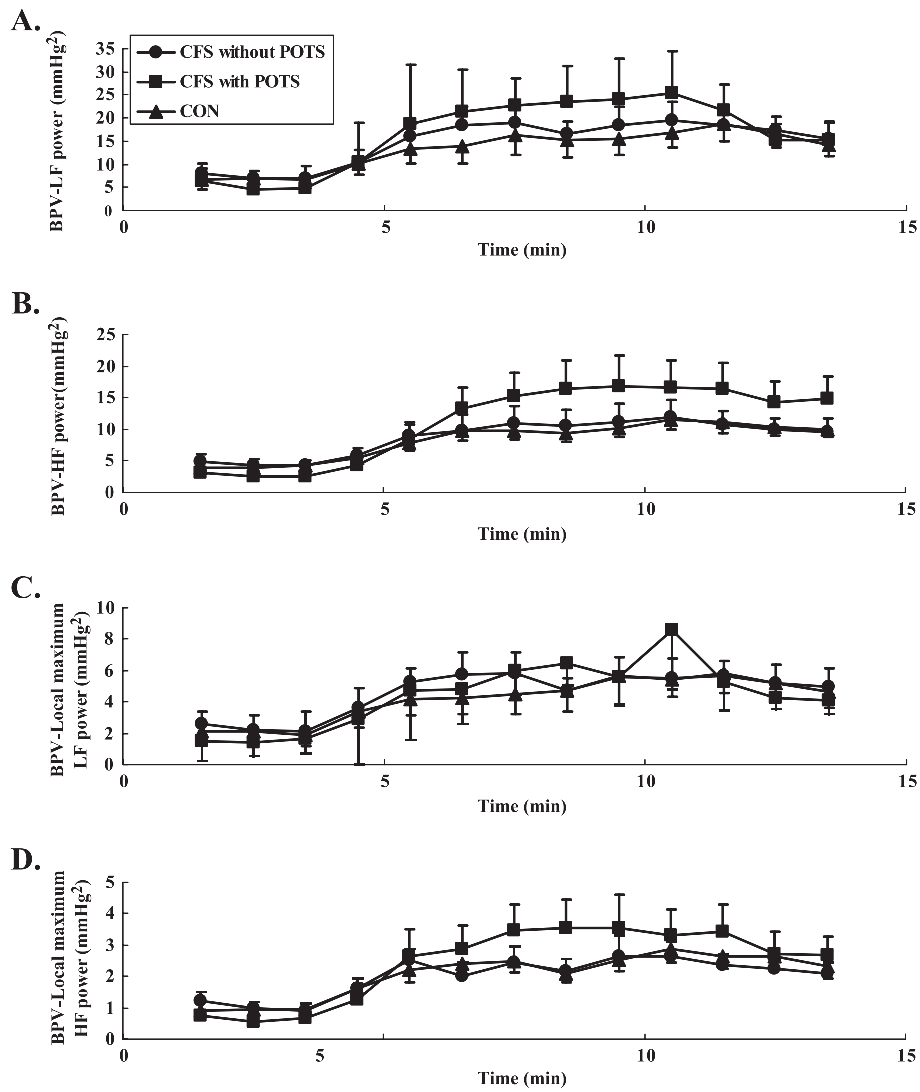

Fig. 4. Group averages of LF (A) and HF (B) power and local maximum power in LF (D) and in HF (E) calculated from blood pressure variability (BPV) using the smoothed pseudo-Wigner-Ville transform (SPWVT) during baseline and head-up tilt in chronic fatigue syndrome (CFS) without postural orthostatic tachycardia syndrome (POTS) (closed circles), CFS patients with POTS (closed squares) and healthy control subjects (closed triangles). There was a significant main effect of time for each variable. Error bars shows S.E.M. of each variable. CON, controls; BPV-LF power, LF power calculated from BPV; BPV-HF, HF power calculated from BPV; BPV-local maximum LF power, local maximum power in LF calculated from BPV; BPV-local maximum HF power, local maximum power in HF calculated from BPV.

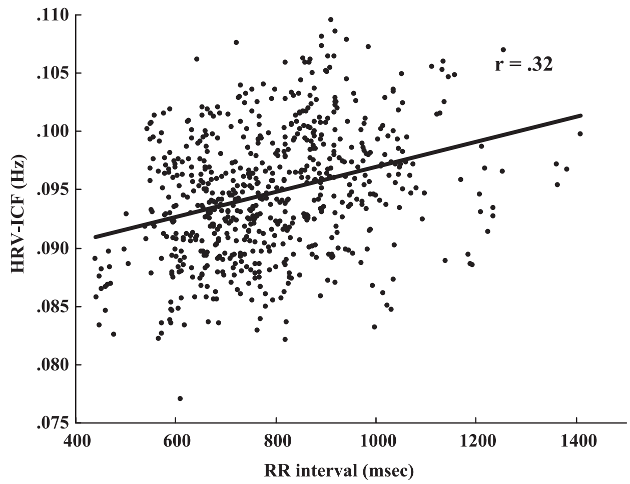

Fig. 5. Correlation between RR intervals and instant center frequency (ICF) in LF calculated from heart rate variability (HRV) using the smoothed pseudo-Wigner-Ville transform (SPWVT). There was a significant correlation between them ($r=0.32$, $p<0.001$). HRV-ICF, instant center frequency calculated from HRV using SPWVT.

($p<0.001$) and HF ($p<0.001$) (Figs. 2 and 4). Apart from these postural effects, there was no group main effects.

In addition, there was a significant interaction of group × time for only one variable: ICF within LF ($p=0.01$, Fig. 2B). This result means that the temporal patterns of ICF differ significantly between CFS patients without POTS and controls. There was also a significant group main effect for SBP ($p=0.006$, Fig. 2D), indicating that SBP in CFS patients with POTS was significantly greater than in controls.

2.2.3. Correlation between ICFS and RR intervals or SBP

There was a significant correlation between ICF calculated from HRV using SPWVT and RR intervals ($r=0.32$, $p<0.001$, Fig. 5) while the correlation between ICF calculated from BPV using SPWVT and SBP was not significant.

3. Discussion

We examined the temporal patterns of cardiac autonomic function just before and just after HUT in CFS patients using SPWVT, which is thought to provide high time and frequency resolution for relatively non-stationary signals (Novak and Novak, 1993; Cerutti et al., 2001).

Although we found no group differences or group × time interactions for most variables, we did find a group × time interaction in the temporal patterns of ICF in LF both from HRV and from BPV just before and just after HUT, which means that temporal patterns of ICF changes during HUT were different between CFS patients without POTS and controls. The physiological meaning of ICF still remains unknown, although ICF was significantly correlated with RR intervals as reported previously (Jasson et al., 1997) and ICF is thought to provide an index of the relationship between sympathetic and vagal activities (Jasson et al., 1997; Baillard et al., 2001). However, the fact that ICF in CFS patients without POTS was different from that in healthy people suggests that it might be a useful diagnostic test; obviously further research is needed to confirm that possibility.

The results of previous studies on changes in cardiac autonomic nervous system function during HUT in adult CFS patients are discrepant (Freeman and Komaroff, 1997; Yataco et al., 1997; De Becker et al., 1998). However, it is difficult to compare the results of this study with the previous ones because the samples in the previous studies heterogeneous comprised of both patients with and without POTS. This heterogeneity could affect group comparisons of autonomic changes induced by HUT (Novak et al., 1996; Stewart, 2000). In addition, previous studies (Yataco et al., 1997; De Becker et al., 1998) used FFT to estimate HRV which is insensitive to rapid autonomic changes induced by HUT (Novak et al., 1996). To our knowledge, this is the first report to use time-frequency analysis to capture autonomic changes during the dynamic phase of HUT in CFS patients.

There were some limitations in this study. First, we did not control respiration and thus have not excluded the possibility that respiration may have influenced results (Sisto et al., 1995). However, because our main findings occurred for ICF in the LF region and because respiration has a greater influence in the HF region, this does not seem to be a likely explanation to our findings. Second, because we did not perform standard autonomic tests, CFS patients even without POTS might have had some autonomic abnormality. Therefore, further studies excluding autonomic abnormalities using standard tests are necessary. Third, we did not assess cardiovagal baroreflex gain. This should be a significant weakness because baroreflex gain is thought to be an important marker of autonomic function. Therefore, further studies on baroreflex gain are necessary. Finally, we used the same subjects to the previous study (LaManca et al., 1999). This could bias the results. Therefore, we need to study a new group of subjects to confirm the results in this study.

4. Conclusion

The data suggest that a subtle underlying disturbance in autonomic function may occur in patients with CFS.

Acknowledgements

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Appendix A

A.1. The Smoothed pseudo-Wigner-Ville transform (SPWVT)

SPWVT was calculated by

$$W(n,m) = \frac{1}{2}N \sum_{k=-N+1}^{N-1} |h(k)|^2 \times \left[\sum_{p=-M+1}^{M-1} g(p) z(n+p+k) z^*(n+p-k) \right] e^{-2i\pi km/N}$$

where $h(\tau)$ is a frequency smoothing window, $g(u)$ is a time smoothing window, and $z(n)$ is a complex signal. A Gaussian window (length of 128 samples, width alpha 2.5) was used as $h(\tau)$ and a rectangular window (length = 64 s) was used as $g(u)$. To avoid an artificial interference between positive and negative frequencies in the Wigner-Ville distribution, the analytic signal has been used that was obtained using Hilbert transform of the original signals.

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