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Decreased fractal component of human heart rate variability during non-REM sleep

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Togo, Fumiharu, and Yoshiharu Yamamoto. Decreased fractal component of human heart rate variability during non-REM sleep. *Am J Physiol Heart Circ Physiol* 280: H17–H21, 2000.—The physiological significance of the fractal component of short-term, spontaneous heart rate variability (HRV) in humans remains unclear. The aim of the present study was to gain further information about the respective fractal components by extracting them from HRV, blood pressure variability (BPV), and instantaneous lung volume (ILV) time series via coarse graining spectral analysis in nine healthy subjects during waking and sleep states. The results show that the contribution made by the fractal component to the total variance in the beat-to-beat R-R interval declined significantly as the depth of non-rapid eye movement (non-REM) sleep increased, that the ILV time series was largely periodic (i.e., nonfractal), and that BPV was unaffected by sleep stage. Finally, the fractal component of HRV during REM sleep was found to be quite similar to that seen during waking. These results suggest that mechanisms involving electroencephalographic desynchronization and/or conscious states of the brain are reflected in the fractal component of HRV.

autonomic nervous system; fractals; coarse graining spectral analysis; rapid eye movement

IN HUMANS beat-to-beat heart rate (HR) variability (HRV), determined from the R-R intervals (RRI), is thought to reflect gross outflow from the autonomic centers in the brain via sympathetic and parasympathetic nervous innervation of pacemaker cells in the sinoatrial node (8). This view is supported by the fact that RRI variability and thus HRV is dramatically reduced in denervated human hearts (e.g., orthotopic heart transplants) (7, 16). HRV is generated in part by periodic inputs of both respiration and blood pressure variability (BPV) into the medullary cardiovascular centers (17). These periodic modulations are clearly identified within the power spectrum of HRV as peaks at the respiratory frequency and at the frequency of the well-known Mayer wave in BPV (8, 17).

Short-term spontaneous HRV also contains an aperiodic component, the power spectrum of which has fractal ($1/f^{\beta}$ type, where f is the frequency and β is the spectral component) scaling (24). Although this fractal component has been reported to account for >70% of the total variance of HRV (24), its physiological significance has not yet been elucidated. We previously demonstrated the dissociation between the fractal components of HRV and BPV (3) and between HRV and instantaneous lung volume (ILV) (22). In that context and considering the possibility that HRV may also be affected by activities of higher centers, such as the limbic system (17, 19), we hypothesized that the fractal component of HRV in humans reflects central, nonreflex autonomic modulation.

In the present study, a sleep model was adopted to test our hypothesis, because the activities in the thalamocortical, reticular activating, and limbic systems are all known to change dramatically during sleep (5, 14). A method called coarse graining spectral analysis (CGSA) (23) was used to extract fractal components from HRV, BPV, and ILV time series. It was found that the contribution of the fractal component of HRV to the total variance significantly declined as the depth of non-rapid eye movement (non-REM) sleep increased; that the ILV time series was largely periodic, i.e., non-fractal; and that BPV was unaffected by sleep stages. Furthermore, the fractal component of HRV during REM sleep was similar to that seen during waking, suggesting that the mechanisms involving an electroencephalographic (EEG) desynchronization and/or conscious states of the brain are reflected in the fractal component of HRV.

METHODS

Protocol. Nine healthy males (mean age 24.5 years) participated in the experiment. The subjects had regular sleeping-waking habits, and none of the subjects were taking any medication at the time of tests. All gave their informed consent to participate in this institutionally approved study after the test protocol was fully described. Each subject underwent 3 nights of polysomnographic (PSG) sessions in a sound-proof, air-conditioned (22–24°C) sleep room. The first and second nights were used for habituation, and data obtained on the third night were used for analysis. The subjects went to bed at the time they normally do and got up voluntarily. In addition, they were instructed that on testing days

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they should refrain from alcohol or caffeine ingestion and avoid napping or engaging in prolonged and/or strenuous exercise in the daytime.

Measurements. EEG (P3-A2, C3-A2), bilateral electrooculograms (EOG; left and right), and mental electromyograms (M-EMG) were monitored continuously throughout the night. The outputs from biological amplifiers (AB601G, Nihon Koden) were recorded with a frequency modulation data recorder (A-69, Sony Magnescale) for later analyses. The sleep stages were manually scored from the PSG recordings by two investigators according to Rechtschaffen and Kales criteria (15). HRV (i.e., beat-to-beat RRI) was monitored using standard bipolar leads with an electrocardiograph (ECG; AT-601G, Nihon Koden). To assess BPV, blood pressure was continuously monitored using a finger cuff (Finapres 2300, Ohmeda), which provided beat-to-beat estimates of systolic blood pressure (SBP). ILV was measured by inductance plethysmography (Respitrace, Non-Invasive Monitoring Systems). The analog output of the ECG meter was differentiated to yield a train of rectangular impulses corresponding to the QRS spikes. The impulse train was processed in real time on a personal computer at a sampling frequency of 1,000 Hz. A customized computer program detected the occurrence of the rectangular impulse and then read the current amplitude in the ILV channel and the subsequent highest value in the blood pressure channel as SBP.

Spectral analysis. Stable, 10-min segments of HRV, BPV and ILV data (600 data points), obtained while the subject was in a supine, waking state before sleep (Awake) and at stages I or II (Light), stages III or IV (Deep), and in REM sleep, were analyzed. Before calculating HRV spectra, we searched the data for extra or missing beats that could affect the results of the spectral analysis. Abnormal intervals were corrected by either omitting (for missing beats) or inserting beats (for doubled or tripled beats). The BPV data were also searched for abnormal values that may have arisen from a servo-reset mechanism of the Finapres; these abnormal values were corrected by linear interpolation. The HRV and BPV data were aligned sequentially with the ILV data interpolated at 4 Hz using a cubic spline function to obtain equally spaced samples. Linear trends were eliminated by linear regression, after which CGSA (23) was used for 10 time-shifted subsets of 512 data points to break down the total power into regular periodic (or harmonic) components and aperiodic (or fractal) components.

Two parameters describing the fractal properties of the signal variability were evaluated with the use of CGSA. First, the percentage of the total power of the signals attributable to random fractal components (%fractal) was calculated; with the use of CGSA, we could discriminate fractal random walks (9) from simple harmonic motions on the basis of the fact that the original and the rescaled (coarse grained) time series had random phase relationships only with fractal signals (23). Second, the fractal component was plotted in a log-power vs. 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 (13). Only the fractal power components within 20% difference from the total power were used for the regression. The recent numerical simulation study (Yamamoto Y and Hughson RL, unpublished results) using markedly different data sets with a mixture of known fractal signals and different types of regular, harmonic signals revealed that the calculated %fractal values by CGSA were generally acceptable for both short-term (including 512 points) and long-term data irrespective of the frequencies of regular signals and the degree of higher harmonics. Also, the estimates for β were found to be influenced by the existence of higher harmonics of regular signals. However, we confirmed this not to be the case for HRV and BPV signals in the present study (see Fig. 2 for the isolated spectral peaks for HRV). The value of β was used to measure the strength of the correlation of the fractal signals. For white noise lacking any time correlation, $\beta = 0$, whereas for ordinary Brownian motion with strong time correlation, $\beta = 2$ (18).

Statistical analyses. Differences among sleep states were assessed using one-way analysis of variance (ANOVA). Post hoc analyses used Tukey's studentized range test to compare means between pairs of states. Bartlett's test for homogeneity of variance, a prerequisite for application of ANOVA, was initially conducted. When rejection of homogeneity of variance occurred, the data were log transformed before being subjected to ANOVA. Differences were considered significant when $P < 0.05$.

RESULTS

Fig. 1 shows representative PSG and HRV recordings obtained while Awake and during Light, Deep, and REM sleep. The HRV waveforms during non-REM sleep were characterized by the absence of the low-frequency "waxing and waning" patterns observed both while Awake and during REM sleep and by almost unchanging high-frequency modulations. In addition, synchronized bursts of EOG with phasic tachycardic responses were identified while Awake and in Light and REM sleep.

The mean RRI was significantly lower in waking than in sleeping subjects, whereas the mean SBP was significantly higher (Table 1). The standard deviation of the RRI, in contrast, was significantly lower during the Deep sleep stage, whereas that for SBP did not vary significantly among conditions (Table 1). Despite the decreased variability in RRI during Deep sleep, the relative contribution made by respiration to the periodic modulation of HRV increased, as shown by the peaks in the normalized total power spectra (Fig. 2). This was accompanied by clear peaks in the normalized ILV spectra, indicating that respiration was regular during non-REM sleep, especially during Deep sleep (Fig. 2). It is of note that the increases in the relative contribution made by respiration to HRV during non-REM sleep was mainly caused by a decrease in the fractal component of HRV (Fig. 3) and not by the increases in the absolute amplitude of the periodic modulations. This was confirmed by the absence of any significant differences in the high-frequency (>0.15 Hz) harmonic power of HRV among different sleep states (Table 1).

The results of CGSA showed that ~70% of the total HRV while Awake and during REM sleep was fractal, whereas the ratio significantly decreased to ~40% during Deep sleep (Fig. 3). The decrease in %fractal was accompanied by a significant decrease in β (Table 1), indicating that the aperiodic component of HRV during Deep sleep was closer to that of white noise. The %fractal for BPV was similar to that for HRV while Awake and during REM sleep but did not change significantly during sleep (Fig. 3). In addition, the values of β remained unchanged at a value closer to

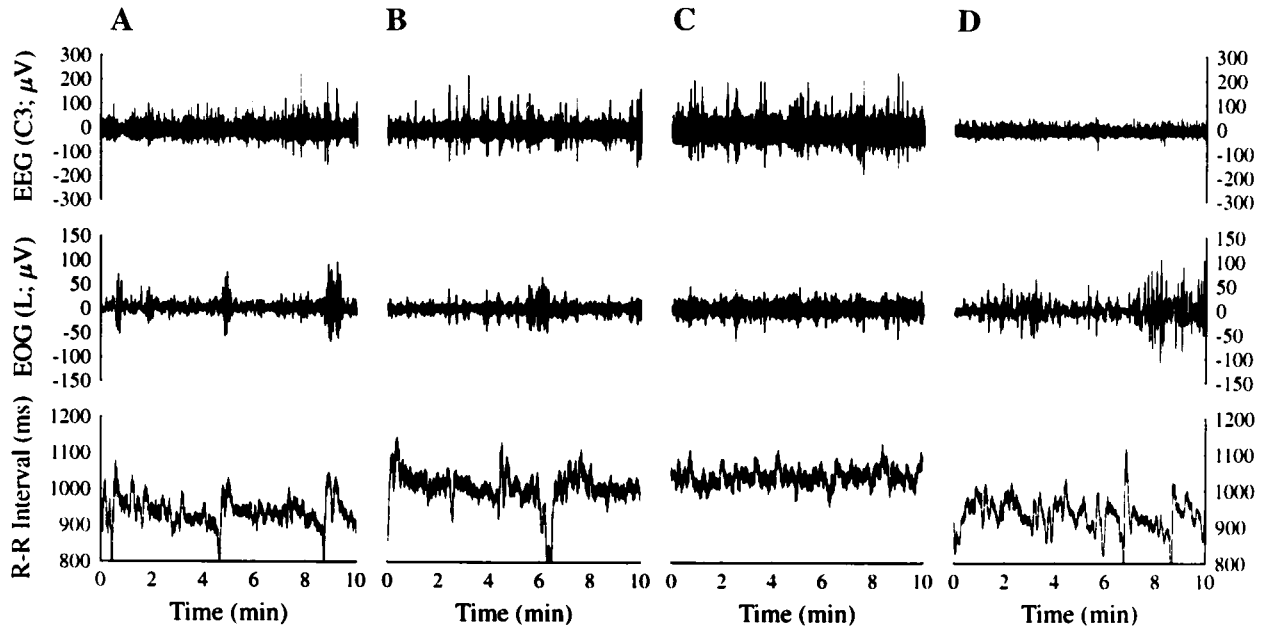

Fig. 1. Representative recordings of polysomnograms and heart rate variability (HRV) obtained while subjects were in a supine, waking state before sleep (Awake; *A*) and during stages I or II (Light; *B*), stages III or IV (Deep; *C*), and rapid eye movement (REM) sleep (*D*). The C3-A2 electroencephalograms (EEG), left (L) electrooculograms (EOG), and R-R intervals (RRI) are shown.

2.0, approximating ordinary Brownian motion (Table 1). The ILV time series was found to be largely periodic, as indicated by the lower %fractal values (Fig. 3). The values during non-REM sleep were significantly lower than those during waking.

DISCUSSION

At the medullary level, variability in the efferent autonomic activity to the heart appears to originate mainly from afferent signaling by arterial baroreceptors because, in unanesthetized cats, sinoaortic denervation dramatically reduces HRV (4). To produce periodic HRV (17), this "basic" variability is further affected by slower variation in both respiration and blood pressure. However, these mechanisms cannot explain the existence of a massive aperiodic, fractal component in human HRV (24). And as shown by previous studies (3, 22) and confirmed by the present findings, the ILV time series does not contain an appreciable fractal component, and the fractal nature of BPV is different from that of HRV. Thus central, nonreflex autonomic modulation may represent an alternative source of the short-term fractal HRV. For example, Spyer (19) proposed a model of reflex inhibition in which the hypothalamus supplies inhibitory, GABAergic innervation to both the nucleus tractus solitaris (the final relay station of baroreceptor afferents) and to vagal cardioinhibitory neurons in the nucleus ambiguus (where respiratory modulation of HR occurs). Moreover, we have shown that a mental stress test slightly but significantly modifies the fractal nature of human HRV (6).

With the use of a sleep model in the present study, we were able to show that brain state substantially affects human HRV and that the changes are seen more clearly in the fractal component than in the periodic components. Similar observations were recently made by Otzenberger et al. (10, 11), who showed that during sleep the dynamics of human HRV are closely related to the EEG mean frequency reflecting the depth of sleep. These investigators used only a gross (harmonic plus fractal) measure for HRV dynamics and did not evaluate the influences of respiratory and blood pressure oscillations on HRV. Consequently, the present findings provide deeper insight into the genesis of HRV by revealing that changes in the fractal component are mediated solely by

Table 1. *Heart rate variability and blood pressure variability*

	Awake	Light	Deep	REM
		Heart rate variability		
mean RRI	1,007 ± 107*	1,072 ± 129	1,075 ± 106	1,026 ± 111
SD_{RRI}	59.1 ± 16.4	63.9 ± 14.1	43.7 ± 10.5†	67.4 ± 19.7
LF_{RRI}	466 ± 341	611 ± 434	171 ± 161	513 ± 417
HF_{RRI}	188 ± 151	407 ± 489	390 ± 256	280 ± 472
β_{RRI}	1.15 ± 0.33	1.26 ± 0.45	0.99 ± 0.35†	1.30 ± 0.35
		Blood pressure variability		
mean SBP	124 ± 17*	112 ± 26	110 ± 15	116 ± 20
SD_{SBP}	8.30 ± 2.26	6.67 ± 4.43	5.82 ± 3.65	6.23 ± 2.02
β_{SBP}	1.53 ± 0.26	1.45 ± 0.45	1.60 ± 0.42	1.61 ± 0.41

Values are means ± SD. Effects of sleep states (Awake, supine, waking state before sleep; Light, stage I or II; Deep, Stages III or IV; REM, rapid eye movement sleep) on individual means and SD of R-R intervals (RRI; in ms) and systolic blood pressure (SBP; in mmHg) variability, high (HF; >0.15 Hz)- and low (LF; <0.15 Hz)-frequency harmonic power of RRI (in ms^2), and the spectral exponents (β). *$P < 0.05$ from the other conditions.

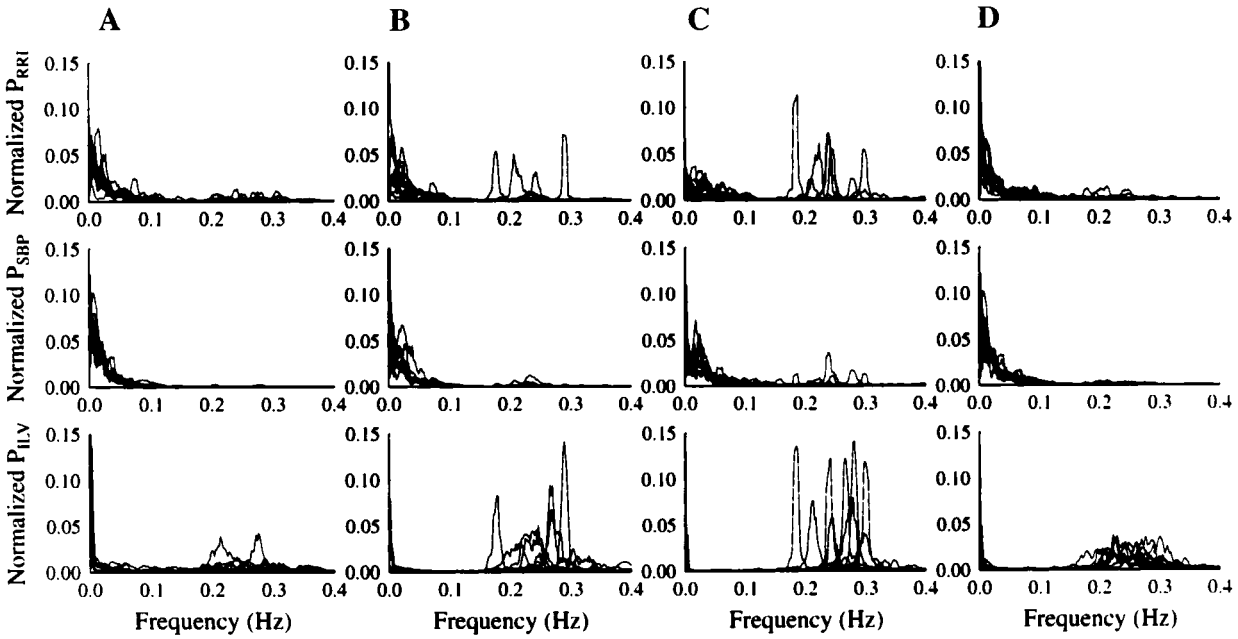

Fig. 2. Power spectra (P) (harmonic plus fractal) of RRI, systolic blood pressure (SBP), and instantaneous lung volume (ILV) normalized to the total integrated spectral power while Awake (*A*) and during Light (*B*), Deep (*C*), and REM sleep (*D*).

higher brain center activity and not by reflex modulations by respiration and blood pressure. The effect of respiration needs to be interpreted cautiously, however, because of technical difficulty in evaluating the absolute changes of ILV throughout the night and the possibility that the regularity in the ILV during non-REM sleep (Fig. 2) results secondarily in the decreased %fractal of HRV. Nonetheless, it is of note that the ILV time series contains no substantial low-frequency oscillation (Fig. 2) that might generate low-frequency fractal HRV by reflex.

As shown also in the present study (Fig. 2), previous studies analyzing HRV during sleep (1, 2, 10, 20) reported that respiratory patterns and the respiratory modulation of HR, i.e., respiratory sinus arrythmia (RSA), became regular during deep sleep. However, the quantitative aspect of RSA, evaluated by the high-frequency spectral power of HRV (8, 17), has not seemed to be established. For example, Bonnet and Arand (2) and Baharav et al. (1) reported the increased high-frequency component of HRV, normalized by the total power of HRV, during deep sleep. In contrast, Vaughn et al. (20) found a decreased high-frequency component during deep sleep without the normalization by the total power. The result of the present study indicated that the absolute amplitude of RSA, reflected by the absolute high-frequency power, did not change (increase) significantly during deep sleep (Table 1), whereas the fractal component of HRV decreased significantly (Fig. 3), together with the insignificant decrease in low-frequency (<0.15 Hz) harmonic power (Table 1). Consequently, if the high-frequency power were normalized by the total power, it would have been overestimated. Thus it can be said that the dramatic change in the aperiodic or fractal component of HRV should be taken into account in evaluating the amplitude of RSA, especially during deep sleep.

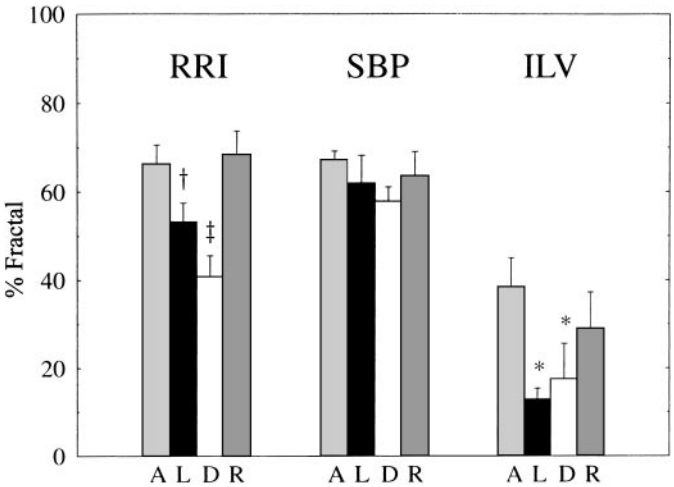

Fig. 3. The percentage of total power of signals attributable to random fractal components (%fractal) values of RRI, SBP, and ILV while Awake (A) and during Light (L), Deep (D), and REM sleep (R). Values are means ± SE. *$P < 0.05$ from A; †$P < 0.05$ from A and R; ‡$P < 0.05$ from A, L, and R.

During sleep, activities in the thalamocortical, reticular activating, and limbic systems change dramatically (5, 14). These changes in neuronal dynamics, which are closely related to EEG synchronization/desynchronization, are also associated with changes in fractal EEG dynamics during sleep (12, 21). For example, in the mecencephalic reticular formation of cats (21), β of the EEG was shown to be lower during slow wave sleep than during waking and REM sleep. A similar decrease in β of fractal HRV during Deep sleep was observed in the

present study (Table 1). In addition, part of the low-frequency modulation of HRV (e.g., occasional and phasic tachycardic responses during waking and REM sleep) was accompanied by bursts of EOG. Thus it is speculated that mechanisms involving EEG desynchronization and/or conscious states of the brain and the associated influences on the limbic system might be responsible for the genesis of the fractal component of HRV. Whereas this hypothesis requires elaboration, it certainly merits further research, because it may open an avenue enabling the study of the states of consciousness in humans through analyses of HRV.

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REFERENCES

1. **Baharav A, Kotagal S, Gibbons V, Rubin BK, Pratt G, Karin J, and Akselrod S.** Fluctuations in autonomic nervous activity during sleep displayed by power spectrum analysis of heart rate variability. *Neurology* 45: 1183–1187, 1995.
2. **Bonnet MH and Arand DL.** Heart rate variability: sleep stage, time of night, and arousal influences. *Electroencephalogr Clin Neurophysiol* 102: 390–396, 1997.
3. **Butler GC, Yamamoto Y, and Hughson RL.** Fractal nature of short-term systolic BP and HR variability during lower body negative pressure. *Am J Physiol Regulatory Integrative Comp Physiol* 267: R26–R33, 1994.
4. **Di Rienzo M, Parati G, Castiglioni P, Omboni S, Ferrari AU, Ramirez AJ, Pedotti A, and Mancia G.** Role of sinoaortic afferents in modulating BP and pulse-interval spectral characteristics in unanesthetized cats. *Am J Physiol Heart Circ Physiol* 261: H1811–H1818, 1991.
5. **Hobson JA, Lydic R, and Baghdoyan HA.** Evolving concepts of sleep cycle generation: from brain centers to neuronal populations. *Behav Brain Res* 9: 371–448, 1986.
6. **Hoshikawa Y and Yamamoto Y.** Effects of Stroop color-word conflict test on the autonomic nervous system responses. *Am J Physiol Heart Circ Physiol* 272: H1113–H1121, 1997.
7. **Hughson RL, Maillet A, Dureau G, Yamamoto Y, and Gharib C.** Spectral analysis of blood pressure variability in heart transplant patients. *Hypertension* 25: 643–650, 1995.
8. **Malliani A, Pagani M, Lombardi F, and Cerutti S.** Cardiovascular neural regulation explored in the frequency domain. *Circulation* 84: 482–492, 1991.
9. **Mandelbrot BB and Van Ness JW.** Fractional Brownian motions, fractional noises and applications. *SIAM Rev* 10: 422–436, 1968.
10. **Otzenberger H, Cronfier C, Simon C, Charloux A, Ehrhart J, Piquard F, and Brandenberger G.** Dynamic heart rate variability: a tool for exploring sympathovagal balance continuously during sleep in men. *Am J Physiol Heart Circ Physiol* 275: H946–H950, 1998.
11. **Otzenberger H, Simon C, Gronfier C, and Brandenberger G.** Temporal relationship between dynamic heart rate variability and electroencephalographic activity during sleep in man. *Neurosci Lett* 229: 173–176, 1997.
12. **Pereda E, Gamundi A, Rial R, and Gonzalez J.** Non-linear behaviour of human EEG: fractal exponent versus correlation dimension in awake and sleep stages. *Neurosci Lett* 250: 91–94, 1998.
13. **Press WH, Flannery BP, Teukolsky SA, and Vetterling WT.** Numerical recipes in C. In: *The Art of Scientific Computing*. Cambridge, UK: Cambridge University Press, 1988.
14. **Pritchard TC and Alloway KD.** *Medical Neuroscience*. Madison, CT: Fence Creek, 1999.
15. **Rechtstchaffen A and Kales A.** *A Manual of Standarized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects*. US Government Printing Office: NIH Publication, Washington DC, 1968.
16. **Sands KE, Appel ML, Lilly LS, Schoen FJ, Mudge JGH, and Cohen RJ.** Power spectrum analysis of heart rate variability in human cardiac transplant recipients. *Circulation* 79: 76–82, 1989.
17. **Saul JP.** Beat-to-beat variations of heart rate reflect modulation of cardiac autonomic outflow. *News Physiol Sci* 5: 32–37, 1990.
18. **Schroeder M.** *Fractals, Chaos, Power Laws: Minutes from an Infinite Paradise*. New York: W. H. Freeman, 1991.
19. **Spyer KM.** Neural mechanisms involved in cardiovascular control during affective behaviour. *Trends Neurosci* 12: 506–513, 1989.
20. **Vaughn BV, Quint SR, Messenheimer JA, and Robertson KR.** Heart period variability in sleep. *Electroencephalogr Clin Neurophysiol* 94: 155–162, 1995.
21. **Yamamoto M, Nakahama H, Shima K, Kodama T, and Mushiake H.** Markov-dependency and spectral analyses on spike-counts in mesencephalic reticular formation during sleep and attentive states. *Brain Res* 366: 279–289, 1986.
22. **Yamamoto Y, Fortrat JO, and Hughson RL.** On the fractal nature of heart rate variability in humans: effects of respiratory sinus arrhythmia. *Am J Physiol Heart Circ Physiol* 269: H480–H486, 1995.
23. **Yamamoto Y and Hughson RL.** Extracting fractal components from time series. *Physica D* 68: 250–264, 1993.
24. **Yamamoto Y and Hughson RL.** On the fractal nature of heart rate variability in humans: effects of data length and β-adrenergic blockade. *Am J Physiol Regulatory Integrative Comp Physiol* 266: R40–R49, 1994.