Psychiatry and Clinical Neurosciences (2003), **57**, 59–65

Regular Article

Correlation between electroencephalography and heart rate variability during sleep

MINA AKO, MT, MMLSc,[1] TOKUHIRO KAWARA, MD, PhD,[1] SUNAO UCHIDA, MD, PhD,[2] SHINICHI MIYAZAKI, MD,[2] KYOKO NISHIHARA, PhD,[2] JUNKO MUKAI, MD,[2] KENZO HIRAO, MD, PhD,[3] JUNYA AKO, MD[4] AND YOSHIRO OKUBO, MD, PhD[1]

[1]*Biofunctional Informatics, Graduate School of Allied Health Sciences, Tokyo Medical and Dental University,* [2]*Department of Sleep Disorders Research, Tokyo Institute of Psychiatry,* [3]*Department of Cardiovascular Medicine, Tokyo Medical and Dental University, Tokyo, Japan and* [4]*Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, USA*

Abstract It is known that autonomic nervous activities change in correspondence with sleep stages. However, the characteristics of continuous fluctuations in nocturnal autonomic nerve tone have not been clarified in detail. The study aimed to determine the possible correlation between the electroencephalogram (EEG) and autonomic nervous activities, and to clarify in detail the nocturnal fluctuations in autonomic nerve activities. Overnight EEGs and electrocardiograms of seven healthy males were obtained. These EEGs were analyzed by fast Fourier transformation algorithm to extract delta, sigma and beta power. Heart rate and heart rate variability (HRV) were calculated in consecutive 5-min epochs. The HRV indices of low frequency (LF), high frequency (HF) and LF/HF ratio were calculated from the spectral analysis of R-R intervals. The sleep stages were manually scored according to Rechtschaffen and Kales' criteria. Low frequency and LF/HF were significantly lower during non-rapid eye movement (NREM) than REM, and were lower in stages 3 and 4 than in stages 1 and 2. Furthermore, delta EEG showed inverse correlations with LF ($r = -0.44$, $P < 0.001$) and LF/HF ($r = -0.41$, $P < 0.001$). In contrast, HF differed neither between REM and NREM nor among NREM sleep stages. Detailed analysis revealed that correlation was evident from the first to third NREM, but not in the fourth and fifth NREM. Delta EEG power showed negative correlations with LF and LF/HF, suggesting that sympathetic nervous activities continuously fluctuate in accordance with sleep deepening and lightening.

Key words delta wave, heart rate variability, sleep electroencephalogram, spectral analysis.

INTRODUCTION

Frequency analysis of oscillation in R-R intervals of electrocardiography (ECG) has been widely applied to assess heart rate variability (HRV) as a marker of autonomic nervous activity.[1,2] Low frequency (LF; 0.04–0.15 Hz) mainly reflects both sympathetic and parasympathetic nervous activities, while high frequency (HF; >0.15Hz) reflects parasympathetic nervous activities.[1–3] In addition, LF/HF is widely used as a relative marker of sympathetic nervous activities or sympathovagal balance.[3,4] It has been established that various cardiovascular disease states are associated with typical changes in HRV.[3] Furthermore, there has been growing interest in autonomic nerve activities assessed by HRV in patients with psychiatric disorders such as panic disorder[5–8] and mood disorder.[9–11]

Autonomic activities as assessed by HRV have been known to show a circadian rhythm.[12] Recently, it has been demonstrated that sleep is characterized by rapid fluctuations in autonomic activities;[13–16] that is to say that HRV was reported to show an increase in HF components and a decrease in LF components in non-rapid eye movement (NREM) stages, and the opposite changes during REM sleep. Low frequency and LF/HF reportedly show a significant decrease as the sleep

Correspondence: Yoshiro Okubo, Biofunctional Informatics, Graduate School of Allied Health Sciences, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan. Email: okubo.psyc@tmd.ac.jp

Received 21 January 2002; revised 10 July 2002; accepted 15 July 2002.

stage deepens. Considering these findings, it is suggested that the sympathetic nervous system is activated during REM sleep, and the parasympathetic nervous system is activated during NREM sleep.

Although HRV indices show continuous fluctuations during sleep, most previous studies compared only the differences in HRV among the categorized sleep stages clarified by Rechtschaffen and Kales' criteria[17] and the details of the dynamics in nocturnal fluctuations of autonomic nerve activities have as yet not been investigated. Examination of the human sleep electroencephalogram (EEG) with fast Fourier transformation (FFT) spectral analysis showed three frequency bands that revealed the characteristic fluctuation patterns throughout the night corresponding to ultradian sleep cycles: delta (0.3–3 Hz), sigma (12–16 Hz) and beta (20–28 Hz) waves.[18–21] Frequency analysis of EEG makes it possible to demonstrate a more detailed sleep structure by examining the continuous alterations of frequency and amplitude of changing EEG waveforms rather than comparing the categorized sleep states. This makes frequency analysis a more suitable method for clarifying the dynamic fluctuations in sleep EEG. Recently, a few studies have investigated the association between EEG spectra and HRV indices.[22–25]

Thus, to elucidate the possible association between EEG and autonomic nerve activity and to clarify nocturnal fluctuations in autonomic nerve activities in detail, we performed frequency analysis of simultaneous recordings of EEG and ECG in young healthy males.

METHODS

Study group

Seven healthy males (24 ± 0.7 years) participated in the study. No high-performance athletes were included. The subjects had normal sinus rhythms and regular sleeping habits, and no subject was medicated with psychoactive agents. All gave their informed consent to their participation. The protocol was approved by the Ethics Committee of the Tokyo Institute of Psychiatry.

Polysomnography recording

Electroencephalogram (F3/A2, C3/A2, C4/A1, O1/A2), monocular electrooculograms, bipolar electromyograms from the chin, and ECG were monitored with Synafit 1000 (NEC, Tokyo, Japan) continuously throughout the night. The outputs from biological amplifiers were recorded with an analog recorder SR-9000 (TEAC, Tokyo, Japan) for later analysis. Each subject underwent two consecutive nights of PSG sessions. The first night was used for habituation, and data obtained from the second night were used for analysis. The subjects were instructed to refrain from alcohol and caffeine ingestion on the test days.

Electroencephalogram data analysis

C3/A2 was used for the frequency analysis of EEG. The data were processed on a personal computer and Pass Plus software (Delta Software, St. Louis, MI, USA). Signals on the analog tape were digitized using a 16-bit AD converter on a Sun SPARCstation at 512 Hz with an antialiasing filter (cut-off frequency, 200–256 Hz). The sleep stages were manually scored at consecutive 20-s intervals from the PSG recordings according to Rechtschaffen and Kales' criteria[17] and EEG delta (0.3–3 Hz), sigma (12–16 Hz) and beta (20–28 Hz) powers were obtained by FFT. Artifacts due to body movements were excluded from the analysis.

Electrocardiography data analysis

The ECG data were processed on a personal computer and Pass Plus software (Delta Software), and signals on the analog tape were digitized by a 16-bit AD converter on a Sun SPARCstation at 128 Hz. GM View (Signalysis, Saitama, Japan) was used to detect the sinus R-R intervals (normal-to-normal, NN). Premature contractions and artifacts caused by movements were omitted from the analysis. A Holter RR system (MemCalc/CHIRAM, Suwa-Trust, Tokyo, Japan) was used for the analysis. Average NN, LF (0.04–0.15 Hz), HF (0.15–0.40 Hz) and LF/HF were calculated every 5 min.

Relations between electroencephalogram and heart rate variability

Differences of HRV indices were assessed among 5-min sleep stages that were decided only when REM or NREM stage was scored at more than 70% of corresponding 20-section intervals. The rounded average of NREM sleep stages (1–4) was used as the 5-min sleep stage.

Pairs of 5-min HRV indices and EEG spectral power averaged among corresponding 20-section intervals were pooled from all subjects in the form of Z-score of each overnight data, and correlation between each of the HRV parameters and EEG frequency powers was assessed. At first the whole night data, including REM as well as NREM, were evaluated in order to obtain a global relationship between EEG and HRV. Then, only the NREM data were assessed to further determine the relationship between the depth of sleep and HRV.

Statistical analysis

Values were expressed as mean ± SE. Differences among sleep stages were assessed using two-way (sleep stage × subject) analysis of variance (ANOVA). When there was a significant difference among sleep stages, post-hoc analysis (Bonferroni's test) was performed to determine how HRV indices differed among sleep stages. Because Bonferroni adjustment was used to avoid errors from multiple tests, differences at $P < 0.05/3$ (HRV indices) = 0.017 were accepted as statistically significant. Pearson's product-moment correlation coefficient was calculated to determine the association between EEG frequency power and HRV indices.

RESULTS

Representative data of EEG and HRV indices from overnight sleep are shown in Fig. 1. Delta EEG showed an increase in NREM and a decrease in REM. Sigma EEG exhibited a transient increase and a subsequent decrease in NREM, and a further decrease in REM. Beta EEG revealed a decrease in NREM and an increase in REM. Similar results were obtained from all subjects.

Comparison of electroencephalogram and heart rate variability indices between REM and NREM sleep

Low frequency was significantly higher during REM (1365.8 ± 77.7 msec^2) than during NREM (1009.5 ± 38.1 msec^2) ($F_{1,567} = 21.88$, $P < 0.0001$). The difference in HF between REM (719.2 ± 49.0 msec^2) and NREM (813.7 ± 29.4 msec^2) was not significant ($F_{1,567} = 4.17$, $P > 0.05/3 = 0.017$). Low frequency/high frequency was significantly higher in REM (2.51 ± 0.17) than in NREM (1.72 ± 0.08) ($F_{1,567} = 19.48$, $P < 0.0001$).

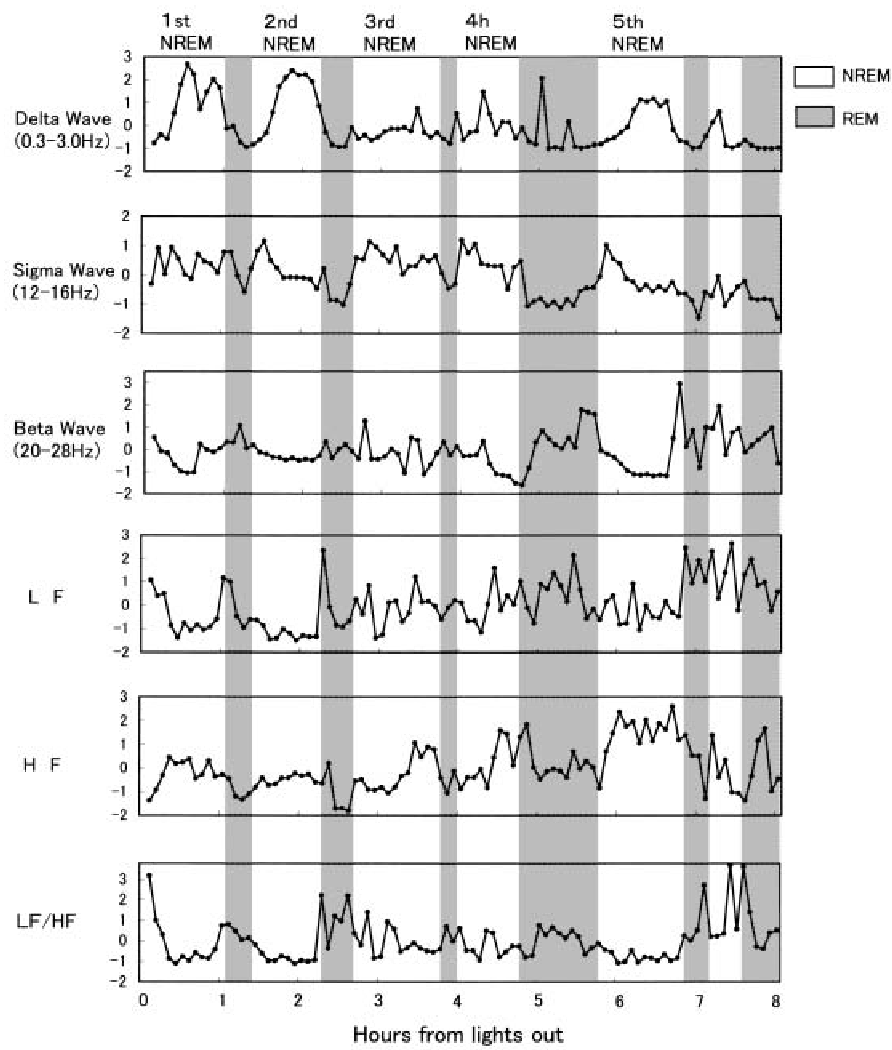

Figure 1. Across-night oscillations of delta (0.3–3 Hz), sigma (12–16 Hz) and beta (20–28 Hz) electroencephalogram spectral power and low frequency (LF), high frequency (HF), LF/HF ratio of heart rate variability in a representative subject. Values were shown in their Z-scores.

Table 1. Comparison of heart rate variability indices in each sleep stage

Sleep stage		Low frequency (msec^2)	High frequency (msec^2)	Low frequency/high frequency
Stage 1	$n=49$	1469.6 ± 133.6	890.2 ± 78.6	2.30 ± 0.29
Stage 2	$n=342$	1055.8 ± 44.7	801.3 ± 35.1	1.85 ± 0.09
Stage 3	$n=56$	569.8 ± 47.9	915.7 ± 85.6	0.78 ± 0.06
Stage 4	$n=19$	284.7 ± 39.1	539.0 ± 109.9	0.86 ± 0.14
REM	$n=115$	1365.8 ± 77.8	719.2 ± 49.0	2.51 ± 0.17
$F_{4,549}$*		16.82	1.89	13.72
P-value		< 0.0001	> 0.05	< 0.0001

* Main effect of sleep stage. Values are expressed as mean ± SE.

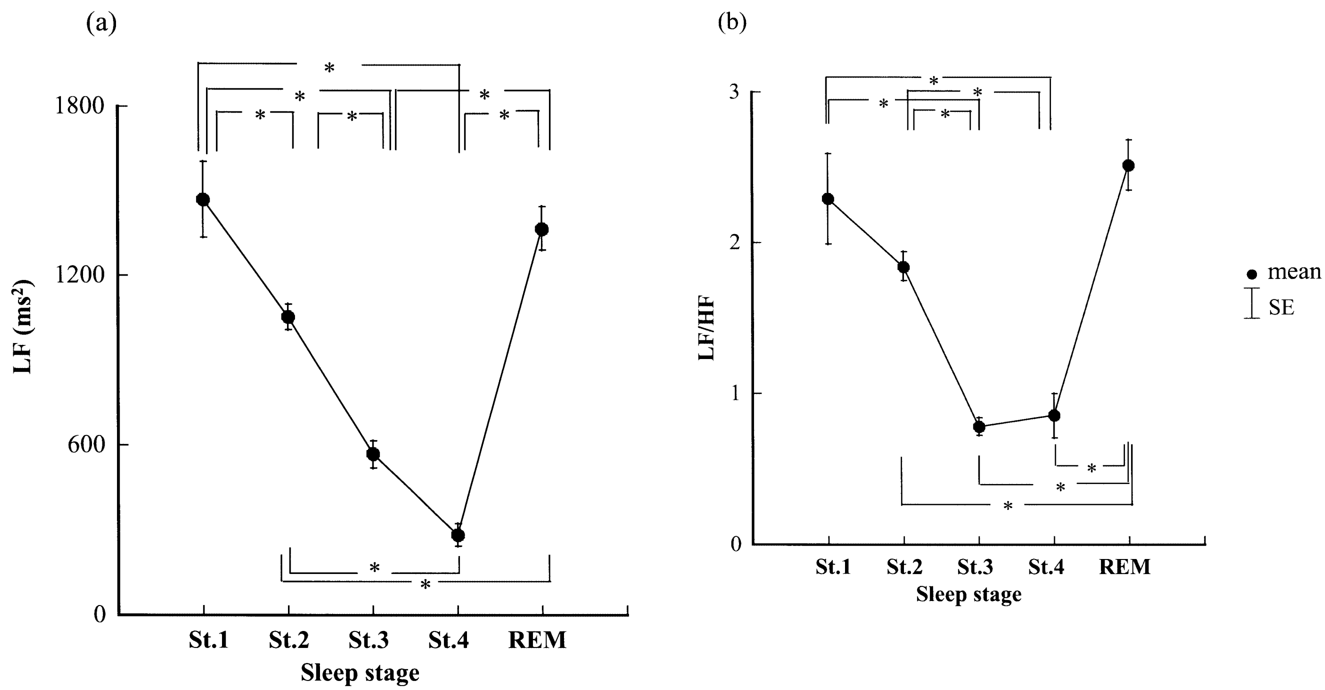

Figure 2. Heart rate variability indices among different sleep stages. (a) Comparison of low frequency (LF) for each sleep stage. (b) Comparison of LF/HF for each sleep stage. * Significant difference by a post-hoc test ($\alpha = 0.05$).

Heart rate variability indices among sleep stages

Table 1 summarizes the results of HRV indices in each sleep stage. Low frequency and LF/HF showed significant differences among sleep stages, but HF did not. Furthermore, post-hoc analysis after two-way ANOVA revealed a significant difference among NREM sleep stages in LF except stage 4 compared to stages 2 and 3 (Fig. 2a), and LF/HF except stage 1 compared to stage 2 and stage 3 compared to stage 4 (Fig. 2b).

Overnight electroencephalogram and heart rate variability indices

Associations between overnight EEG frequency power and the respective HRV indices are summarized in Table 2. Only delta EEG showed inverse correlations with LF (Fig. 3a, $r = -0.44$, $P < 0.001$) and LF/HF (Fig. 3b, $r = -0.41$, $P < 0.001$). The other EEG factors showed no significant correlation with any of the HRV indices.

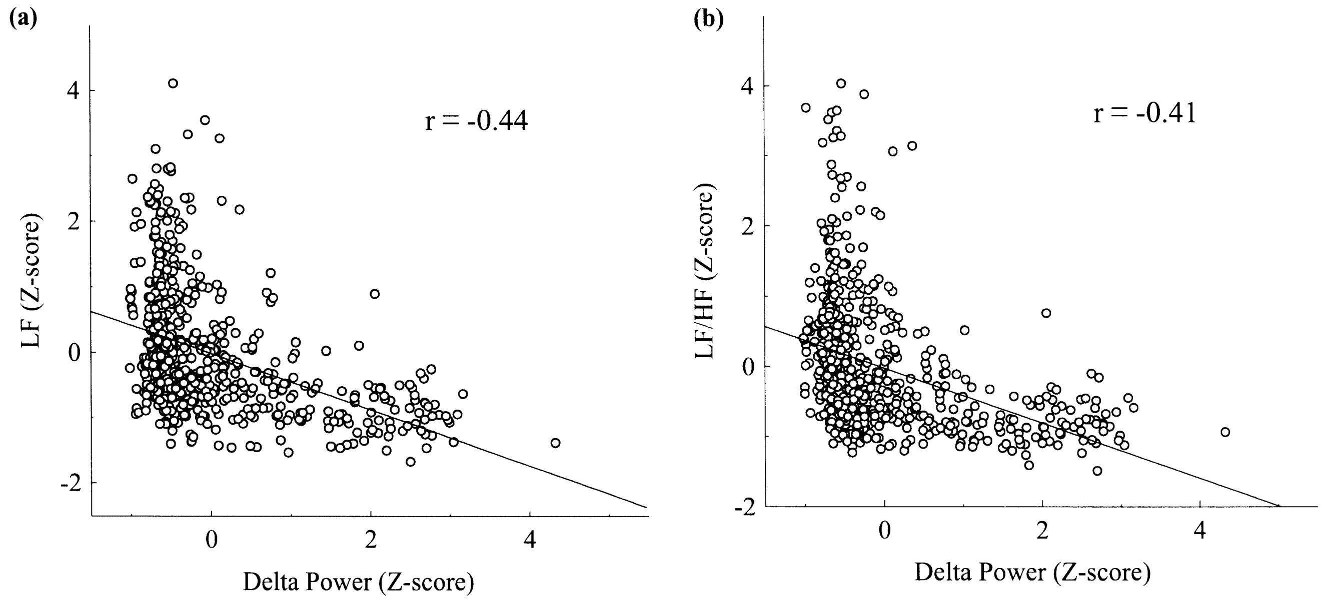

Figure 3. Correlation between delta power and heart rate variability in one night. (a) Negative correlation between delta power and low frequency (LF) ($r = -0.44$, $P < 0.001$). (b) Negative correlation between delta power and LF/HF ($r = -0.41$, $P < 0.001$).

Table 2. Correlation coefficients between spectral power and heart rate variability in sleep

	Low frequency	High frequency	Low frequency/ high frequency
Delta power	−0.44*	0.04	−0.41*
Sigma power	−0.16	0.01	−0.16
Beta power	0.24	−0.14	0.29

* $P < 0.001$.

Electroencephalogram and heart rate variability indices in each sleep cycle

Electroencephalogram frequency power and each of the HRV indices were also analyzed in each specified (first to fifth) NREM sleep cycle, and their results are summarized in Table 3. Sigma EEG power did not correlate with HRV indices in any of the ultradian sleep cycles. Beta EEG negatively correlated with HF only in the fifth NREM. Delta EEG showed inverse correlations with LF and LF/HF from the first to third NREM, but not in the fourth and fifth NREM.

DISCUSSION

Overnight EEG and ECG were investigated in seven young healthy males to elucidate the possible association between EEG and autonomic nerve activity during sleep. Comparisons of HRV indices among different sleep stages revealed that LF and LF/HF were lower in NREM sleep than in REM sleep. Furthermore, there were significant differences in LF and LF/HF among NREM sleep stages; LF and LF/HF were lower in stages 3 and 4 than in stages 1 and 2. These findings were in line with previous findings of LF and LF/HF changes among sleep stages.[13,14,16,26] In contrast, there have been inconsistent results for HF fluctuation during sleep, that is, one reported a decrease[26] and others reported an increase[13,14,16] with sleep deepening. We found no significant differences either in HF between REM and NREM or among different sleep stages in the present study.

Most previous studies[13–15,26] focused on the differences in HRV indices only among awake, NREM sleep and REM sleep, or within categorized sleep stages. Describing sleep EEG only as a series of discrete sleep stages would overlook the continuous oscillatory process of sleep, while quantitative EEG analysis would allow clarification of the HRV fluctuations during sleep in detail. However, there have been only a few studies to date that have investigated the association between quantitative EEG indices and autonomic nerve tone.[22–25] Furthermore, correlations of HRV indices have been investigated with only limited EEG variables, such as the mean frequency of the global EEG band (0.5–35 Hz),[22,23] alpha EEG frequency,[24] and delta

Table 3. Correlation coefficients between electroencephalogram and heart rate variability in each sleep cycle

			Low frequency	High frequency	Low frequency/high frequency
Delta power	1st NREM	$n = 151$	−0.52*	0.09	−0.48*
	2nd NREM	$n = 95$	−0.43*	−0.05	−0.43*
	3rd NREM	$n = 87$	−0.44*	0.06	−0.44*
	4th NREM	$n = 78$	−0.34	0.25	−0.39
	5th NREM	$n = 28$	−0.16	0.10	−0.18
Sigma power	1st NREM	$n = 151$	0.10	−0.08	0.12
	2nd NREM	$n = 95$	0.29	0.11	0.19
	3rd NREM	$n = 87$	0.14	0.02	0.03
	4th NREM	$n = 78$	0.09	−0.01	−0.01
	5th NREM	$n = 28$	−0.10	−0.25	0.06
Beta power	1st NREM	$n = 151$	0.30	0.06	0.23
	2nd NREM	$n = 95$	0.36	0.13	0.20
	3rd NREM	$n = 87$	0.21	−0.14	0.25
	4th NREM	$n = 78$	−0.06	−0.33	0.25
	5th NREM	$n = 28$	0.14	−0.42*	0.39

* $P < 0.001$.

EEG power.[25] In the present study, we compared the nocturnal fluctuations in quantitative EEG indices of delta, sigma and beta bands, and those in HRV indices. As a consequence, we found that delta EEG showed inverse correlations with LF ($r = -0.44$, $P < 0.001$) and LF/HF ($r = -0.41$, $P < 0.001$), although sigma and beta EEG did not show any correlation. Interestingly, a recent study[25] has reported an inverse correlation between delta wave activity and LF/(LF+HF) ratio, and this is expected to reflect the sympathovagal balance. Considering that we did not find any correlation between HF and EEG, the inverse correlation of LF with delta EEG may be essential, suggesting that sympathetic nervous activities were decreasing with sleep deepening and increasing with sleep lightening.

Delta EEG is abundant during NREM sleep but absent during REM; it is also more prominent in earlier NREM periods among overnight sleep cycles. To the best of our knowledge, there have been no studies on the association between EEG and HRV among different sleep cycles. We investigated the association in each ultradian sleep cycle and found that delta EEG correlated well with LF and LF/HF during the first to third NREM sleep, and that the correlation was lost in the fourth and fifth NREM. The disappearance of inverse correlation in the late sleep cycles may be attributable to the circadian autonomic change as suggested in recent studies.[27,28] In the present study, we analyzed only data from one night from each subject to clarify the nocturnal fluctuations in HRV. According to our limited analysis of the one-night data, it is impossible to draw conclusions about the possible effect of circadian oscillation on HRV.

It is still unclear why the autonomic nervous activities and EEG show such correlations. However, the distinct inverse correlation at least suggests a common central mechanism underlying EEG and HRV. This mechanism should be the subject of future studies.

Autonomic nervous activities have various effects on the pathogenesis of diseases such as cardiovascular diseases.[3] Cardiovascular diseases could be influenced by intervention directed toward the modulation of sleep. Thus, studies on human sleep can be expected to have greater clinical relevance in cardiovascular medicine. Heart rate variability indices also have been used as a safe, non-invasive, and efficient way to assess autonomic nerve activities in patients with panic disorder[5–8] and mood disorder.[9–11] However, only a few studies took account of nocturnal fluctuations of HRV.[7,8] Our present findings suggest that future studies should investigate HRV in psychiatric patients in relation to their changes in sleep structure.

CONCLUSIONS

To clarify the continuous fluctuations of autonomic nervous activities during sleep, we investigated the association between HRV and EEG using frequency analysis of PSG. Although sigma and beta EEGs were not correlated, delta EEG was inversely correlated with LF and LF/HF, suggesting that sympathetic nervous activities became decreased with sleep deepening and increased with sleep lightening. The continuous evaluation of HRV and EEG seems to provide an attractive approach for new research on autonomic nerve activities in psychiatric disorders.

ACKNOWLEDGMENTS

Ms Mayumi Futamata is greatly acknowledged for her analytical support. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology and the research grant for nervous and mental disorders from the Ministry of Health, Labor and Welfare of Japan (11B-3).

REFERENCES

1. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. *Science* 1981; **213**: 220–222.
2. Pomeranz B, Macaulay RJ, Caudill MA *et al.* Assessment of autonomic function in humans by heart rate spectral analysis. *Am. J. Physiol.* 1985; **248**: H151–H153.
3. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation* 1996; **93**: 1043–1065.
4. Malliani A, Lombardi F, Pagani M. Power spectrum analysis of heart rate variability: a tool to explore neural regulatory mechanisms. *Br. Heart J.* 1994; **71**: 1–2.
5. Ito T, Inoue Y, Sugihara T, Yamada H, Katayama S, Kawahara R. Autonomic function in the early stage of panic disorder: power spectral analysis of heart rate variability. *Psychiatry Clin. Neurosci.* 1999; **53**: 667–672.
6. Yeragani V, Sobolewski E, Igel G, Johnson C. Decreased heart-period variability in patients with panic disorder. a study of Holter ECG records. *Psychiatry Res.* 1998; **78**: 89–99.
7. Sloan E, Natarajan M, Baker B *et al.* Nocturnal and daytime panic attacks — comparison of sleep architecture, heart rate variability, and response to sodium lactate challenge. *Biol. Psychiatry* 1999; **45**: 1313–1320.
8. McCraty R, Atkinson M, Tomasino D, Stuppy W. Analysis of twenty-four hour heart rate variability in patients with panic disorder. *Biol. Psychol.* 2001; **56**: 131–150.
9. Carney R, Blumenthal J, Stein P *et al.* Depression, heart rate variability, and acute myocardial infarction. *Circulation* 2001; **104**: 2024–2028.
10. Rechlin T, Weis M, Spitzer A, Kaschka W. Are affective disorders associated with alterations of heart rate variability? *J. Affect. Disord.* 1994; **32**: 271–275.
11. Yeragani V, Balon R, Pohl R, Ramesh C. Depression and heart rate variability. *Biol. Psychiatry* 1995; **38**: 768–770.
12. Huikuri HV, Kessler KM, Terracall E, Castellanos A, Linnaluoto MK, Myerburg RJ. Reproducibility and circadian rhythm of heart rate variability in healthy subjects. *Am. J. Cardiol.* 1990; **65**: 391–393.
13. Tsunoda M, Endo T, Hashimoto S, Honma S, Honma K. Effects of light and sleep stages on heart rate variability in humans. *Psychiatry Clin. Neurosci.* 2001; **55**: 285–286.
14. Bonnet MH, Arand DL. Heart rate variability: sleep stage, time of night, and arousal influences. *Electroencephalogr. Clin. Neurophysiol.* 1997; **102**: 390–396.
15. Vanoli E, Adamson PB, Ba L, Pinna GD, Lazzara R, Orr WC. Heart rate variability during specific sleep stages. A comparison of healthy subjects with patients after myocardial infarction. *Circulation* 1995; **91**: 1918–1922.
16. Scholz U, Bianchi A, Cerutti S, Kubicki S. Vegetative background of sleep: spectral analysis of the heart rate variability. *Physiol. Behav.* 1997; **62**: 1037–1043.
17. Rechtschaffen A, Kales A. *Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects*. US Government Printing Office, Washington DC, 1968.
18. Nakabayashi T, Uchida S, Maehara T *et al.* Absence of sleep spindles in human medial and basal temporal lobes. *Psychiatry Clin. Neurosci.* 2001; **55**: 57–65.
19. Uchida S, Maloney T, Feinberg I. Beta (20–28 Hz) and delta (0. 3–3 Hz) EEGs oscillate reciprocally across NREM and REM sleep. *Sleep* 1992; **15**: 352–358.
20. Uchida S, Maloney T, Feinberg I. Sigma (12–16 Hz) and beta (20–28 Hz) EEG discriminate NREM and REM sleep. *Brain Res.* 1994; **659**: 243–248.
21. Uchida S, Feinberg I, March JD, Atsumi Y, Maloney T. A comparison of period amplitude analysis and FFT power spectral analysis of all-night human sleep EEG. *Physiol. Behav.* 1999; **67**: 121–131.
22. Otzenberger H, Simon C, Gronfier C, Brandenberger G. Temporal relationship between dynamic heart rate variability and electroencephalographic activity during sleep in man. *Neurosci. Lett.* 1997; **229**: 173–176.
23. Otzenberger H, Gronfier C, Simon C *et al.* Dynamic heart rate variability: a tool for exploring sympathovagal balance continuously during sleep in men. *Am. J. Physiol.* 1998; **275**: H946–H950.
24. Ehrhart J, Toussaint M, Simon C, Gronfier C, Luthringer R, Brandenberger G. Alpha activity and cardiac correlates: three types of relationships during nocturnal sleep. *Clin. Neurophysiol.* 2000; **111**: 940–946.
25. Brandenberger G, Ehrhart J, Piquard F, Simon C. Inverse coupling between ultradian oscillations in delta wave activity and heart rate variability during sleep. *Clin. Neurophysiol.* 2001; **112**: 992–996.
26. Vaughn B, Quint S, Messenheimer J, Robertson K. Heart period variability in sleep. *Electroencephalogr. Clin. Neurophysiol.* 1995; **94**: 155–162.
27. Burgess HJ, Trinder J, Kim Y, Luke D. Sleep and circadian influences on cardiac autonomic nervous system activity. *Am. J. Physiol.* 1997; **273**: H1761–H1768.
28. Trinder J, Kleiman J, Carrington M *et al.* Autonomic activity during human sleep as a function of time and sleep stage. *J. Sleep Res.* 2001; **10**: 253–264.