Clin. Cardiol. 21, 271–276 (1998)

# Circadian Rhythm of Autonomic Activity in Patients with Obstructive Sleep Apnea Syndrome

AKIKO NODA, PH.D., FUMIHIKO YASUMA, M.D., FCCP, TAMOTSU OKADA, M.D., PH.D., MITSUHIRO YOKOTA, M.D., PH.D., FACC

Nagoya University School of Health Sciences, Nagoya University College of Medical Technology, Department of Clinical Laboratory Medicine, The First Department of Internal Medicine, Nagoya University Hospital, Nagoya, Japan

## Summary

*Background and hypothesis:* Although the immediate effects of sleep apnea on hemodynamics and the neurological system have been studied, little is known about the circadian rhythm of heart rate variability in patients with obstructive sleep apnea syndrome (OSAS). The purpose of the present study was to investigate the effects of sleep apnea on the autonomic activity during daytime, which may play some role in the pathogenesis of cardiovascular complications in OSAS.

*Methods:* We studied 18 middle-aged male patients with OSAS and 10 age-matched control subjects. Patients with OSAS were classified according to the severity of OSAS: patients with an apnea index (AI) < 20 were considered to have mild OSAS (Group 1, n = 8) and patients with an AI ≥ 20 were considered to have severe OSAS (Group 2, n = 10). Heart rate variability was calculated from the 24-h ambulatory electrocardiograms by the Fourier transformation. Power spectra were quantified at 0.04–0.15 Hz [low frequency power (LF)ln($ms^2$)] and 0.15–0.40Hz [high frequency power (HF)ln($ms^2$)]. The HF component and the ratio of LF to HF were used as indices of the parasympathetic and sympathetic activity, respectively.

*Results:* The circadian rhythms of the LF, HF, and LF/HF ratio differed significantly in Group 2 compared with Group 1 and control subjects ($p < 0.05$). Hypertension (>160/95 mm Hg) was found in 7 (70.0%) of 10 patients in Group 2, and in 1 (12.5%) of 8 patients in Group 1. Echocardiographic evidence of left ventricular hypertrophy (LVH) (an interventricular septal thickness or a left ventricular posterior wall thickness ≥ 12 mm) was found in 3 (30.0%) of 10 patients in Group 2, and in 1 (12.5%) of 8 patients in Group 1. The mean HF from 4 A.M. to 12 noon was significantly lower in Group 2 than in Group 1 and the control group, and it correlated significantly with the lowest nocturnal $SaO_2$ ($r = 0.58$, $p < 0.05$). The mean LF/HF ratio during the same period was significantly higher in Group 2 than in Group 1 and the control group, and it correlated significantly with total time of the nocturnal oxygen saturation < 90% ($r = 0.64$, $p < 0.005$) and the lowest nocturnal $SaO_2$ ($r = 0.56$, $p < 0.05$). Ventricular tachycardia was found in the early morning in one patient, ST-T depression in two patients, and sinus arrest in two patients in Group 2.

*Conclusion:* These findings suggest that sleep-disordered breathing associated with severe oxygen desaturation might influence heart rate variability not only during sleep but also during daytime. OSAS per se might contribute to altered circadian rhythm in autonomic activity leading to the development of cardiovascular diseases.

**Key words:** sleep apnea, autonomic activity, heart rate, spectral analysis, oxygen saturation, hypertension

## Introduction

Obstructive sleep apnea syndrome (OSAS) is characterized by recurrent episodes of apnea during sleep. These episodes have an immediate effect on the respiratory, circulatory, and central nervous systems.[1,2] Untreated patients with this syndrome have a poorer prognosis than patients who undergo tracheostomy.[3] The high morbidity and mortality rates associated with severe OSAS are mostly attributed to the coexistence of various cardiovascular diseases.[4–6] The previous epidemiologic studies have shown that snoring, which is characteristic of OSAS, is a risk factor for hypertension, angina pectoris,[7–9] and cerebral infarction,[10] but the cause and mechanism of these associations are not clearly understood.

Address for reprints:

Mitsuhiro Yokota, M.D., Ph.D., FACC
Cardiovascular Section
Department of Clinical Laboratory Medicine
Nagoya University Hospital
Tsurumai-cho, Showa-ku
Nagoya 466, Japan

Received: September 10, 1997
Accepted with revision: January 6, 1998

Arousal, hypoxia, sleep fragmentation, and loss of slow-wave sleep may affect the cardiovascular autonomic activities and hemodynamic control in patients with OSAS,[11–13] contributing to the poor prognosis for patients with severe OSAS.[3–5] Although heart rate variability is decreased and this decrease is associated with a high mortality rate in patients with coronary artery disease,[14–16] little is known about the circadian variation of autonomic activity in patients with OSAS.

While the lack of appropriate techniques has limited our ability to assess the autonomic activity in humans, the spectral analysis of heart rate variability, which was introduced to quantify the cardiac autonomic activity[17, 18] is gaining popularity in clinical research.[19–26] We investigated the role of circadian variations in autonomic activity in patients with OSAS using the spectral analysis of heart rate variability with 24-h ambulatory electrocardiography (ECG) to determine whether the OSAS per se influences circadian rhythm of autonomic activity.

## Methods

### Subjects

We studied 18 male patients with OSAS (age 43–76 years, mean 55.9 years) and 10 healthy men without OSAS (age 45–65 years, mean 53.2 years) as age-matched controls. The control subjects, who were of almost ideal body weight, did not have cardiovascular or respiratory complications. Patients with OSAS were classified according to the severity of the disease:[4] patients with an apnea index (AI) < 20 were considered to have mild OSAS (Group 1, n = 8) and patients with an AI ≥ 20 were considered to have severe OSAS (Group 2, n = 10). Left ventricular hypertrophy (LVH) and cardiac function were evaluated using echocardiography. Left ventricular hypertrophy was defined as an interventricular septal thickness or a left ventricular posterior wall thickness ≥12 mm.

### Data Acquisition and Analysis of Heart Rate Variability

All subjects underwent 24-h ambulatory ECG with a Holter monitor (Marquette Electronics, Inc., Milwaukee, Wis.), using bipolar $CM_5$ (standard $V_5$ lead position) and $CC_5$ leads. During monitoring, the subjects were instructed to perform their daily routines and to keep a diary of their symptoms and physical activities (waking, sleeping, exercise, etc.).

Power spectral analysis was performed with the Marquette 8000/T system and R-R interval analysis software (version 002A). QRS complexes were identified and only normal-to-normal (NN) intervals were analyzed. The hourly power spectra data were determined as the average of 30 spectra over 2 min periods and the results were calculated by the 256 point Fourier transformation. Marquette spectral measures were computed hourly, and the overall average of the test duration was determined. These data were quantified by area in two frequency bandwidths: 0.04 to 0.15 Hz [low frequency (LF) power]: LF $\ln(ms^2)$, and 0.15 to 0.40 Hz [high-frequency (HF) power]: HF $\ln(ms^2)$, and were expressed in units of $ms^2$ (squared amplitude). These values were then transformed in a log scale. The HF power expresses parasympathetic activity, and the ratio of low-to-high frequency power (LF/HF) reflects the sympathetic activity, respectively.[17, 18]

### Sleep Parameters

The standard polysomnography (PSG) with pulse oximetry (Pulsox 7, Minolta Co, Ltd, Toyko, Japan) was performed in 18 patients with OSAS. Electroencephalogram (EEG) (C3-O1, O4-A1), electro-oculogram, electromyograms, and ECGs were continuously recorded and respiration was monitored with an oronasal thermistor and a thoracoabdominal strain gauge. An apneic episode was defined as a cessation of airflow at the mouth and the nose lasting >10 s. We also calculated the AI [total number of apnea/total sleep time (h)]. OSAS was defined as 30 or more apneic episodes over a 7 h period of sleep during both REM and non-REM sleep, and AI ≥5.[27] Total time of the nocturnal oxygen saturation below 90% (time of $SaO_2 < 90\%$) and lowest $SaO_2$ during sleep were determined by pulse oximetry.

### Statistics

The results are expressed as mean ± standard deviation (SD). Data were analyzed by ANOVA, and a p value $< 0.05$ was considered statistically significant. A periodic regression curve of the 24-h power spectral density was derived by Fourier transformation, and the level and pattern of the curve were assessed by periodic analysis of covariance.[28]

## Results

There were no significant differences in age and body height between Groups 1 and 2 (Table I). The incidence of obesity, body weight, prevalence of hypertension (>160/95 mmHg), and the AI were significantly higher in Group 2 than in Group 1. Time of $SaO_2$ <90% was significantly longer in Group 2 than in Group 1. Based on the patients' diaries, there was no significant difference in their daily routines, that is, the times at which they woke or slept, or in total sleep time. The levels of the physical and mental activity were similar in both groups.

There was no significant difference among Groups 1 and 2 and the control subjects in the parameters of 24 h heart rate variability (Table II). The periodic regression curves of the 24 h LF, HF, and LF/HF ratio in the subjects were statistically reliable ($p < 0.001$) (Fig. 1). In the control subjects, HF peaked at 3 A.M., and then decreased until 9 A.M. The HF remaintained stable throughout the day, reaching its nadir at 7 to 8 P.M. Although LF peaked at about 3 to 4 A.M., there was no significant difference between nighttime and daytime in the level of LF. The nadir of the LF/HF ratio occurred at 3 to 4 A.M. The LF/HF ratio increased progressively until it peaked at about 7 to 8 P.M. There was no significant difference between Group 1

TABLE I Features in obstructive sleep apnea syndrome

| Apnea index | Group 1 <20 n=8 | Group 2 ≥20 n=10 | p Value |
|---|---|---|---|
| Age (years) | 58.6±9.87 | 53.9±8.27 | NS |
| Height (cm) | 166±7.74 | 163±2.59 | NS |
| Weight (kg) | 67.5±12.0 | 78.7±8.77 | <0.05 |
| Obesity index (Broca) (%) | 12.7±11.1 | 38.2±14.6 | <0.005 |
| Prevalence of HT (%) | 12.5 | 70.0 | <0.05 |
| Prevalence of LVH (%) | 12.5 | 30.0 | NS |
| No. of apneas | 84.1±40.4 | 347±124 | <0.001 |
| Apnea index (/h) | 11.9±4.69 | 43.7±16.1 | <0.001 |
| Lowest $SaO_2$ (%) | 78.3±10.2 | 63.1±9.83 | <0.01 |
| Time of $SaO_2$ < 90% (min) | 16.9±20.0 | 98.4±43.7 | <0.001 |

Values are given mean ± SD.
Apnea index = number of apneas per hour. Time of $SaO_2$ < 90% = total time of the nocturnal oxygen saturation <90%.
*Abbreviations:* HT = hypertension, LVH = left ventricular hypertrophy, NS = not significant, SD = standard deviation.

TABLE II Comparison of LF, HF, LF/HF and mean NN between age-matched control subjects and patients with obstructive sleep apnea syndrome

| | Group C | Group 1 AI<20 | Group 2 AI≥20 |
|---|---|---|---|
| 24-hour average | | | |
| LF [ln($ms^2$)] | 5.76±0.58 | 5.52±0.54 | 5.63±0.69 |
| HF [ln($ms^2$)] | 4.46±0.56 | 4.51±0.80 | 4.23±0.66 |
| LF/HF | 1.31±0.11 | 1.27±0.09 | 1.34±0.12 |
| Mean NN (ms) | 863±57.5 | 830±117 | 765±93.5 |
| From 4 A.M. to 12 noon | | | |
| LF [ln($ms^2$)] | 5.80±0.67 | 5.69±0.72 | 5.20±0.72 |
| HF [ln($ms^2$)] | 4.50±0.58 | 4.51±0.84 | 3.80±0.57[a, b] |
| LF/HF | 1.30±0.09 | 1.28±0.11 | 1.40±0.10[a, b] |
| Mean NN (ms) | 881±62.4 | 880±75.0 | 741±163[a, b] |

[a] $p < 0.05$ controls (Group C) vs. Group 2.
[b] $p < 0.05$ Group 1 vs. Group 2.
*Abbreviations:* mean NN = mean of all RR intervals between normal beats. Other abbreviations as in Table I.

and control group in the circadian rhythms of LF, HF, and LF/HF ratio (Fig. 1).

In Group 2, LF and HF peaked at about 2 A.M. and then decreased until 9 A.M. The LF and HF were stable throughout the day until 7 to 8 P.M., when they began to increase, and continued to increase until 2 A.M. The nadir of LF and HF were significantly lower in Group 2. The nadir in LF/HF ratio occurred soon after the onset of sleep (about 1 to 2 A.M.). The LF/HF ratio increased progressively, peaking at 9 A.M., remained stable throughout the day, and then decreased until 1 to 2 A.M. The circadian rhythms of LF, HF, and LF/HF

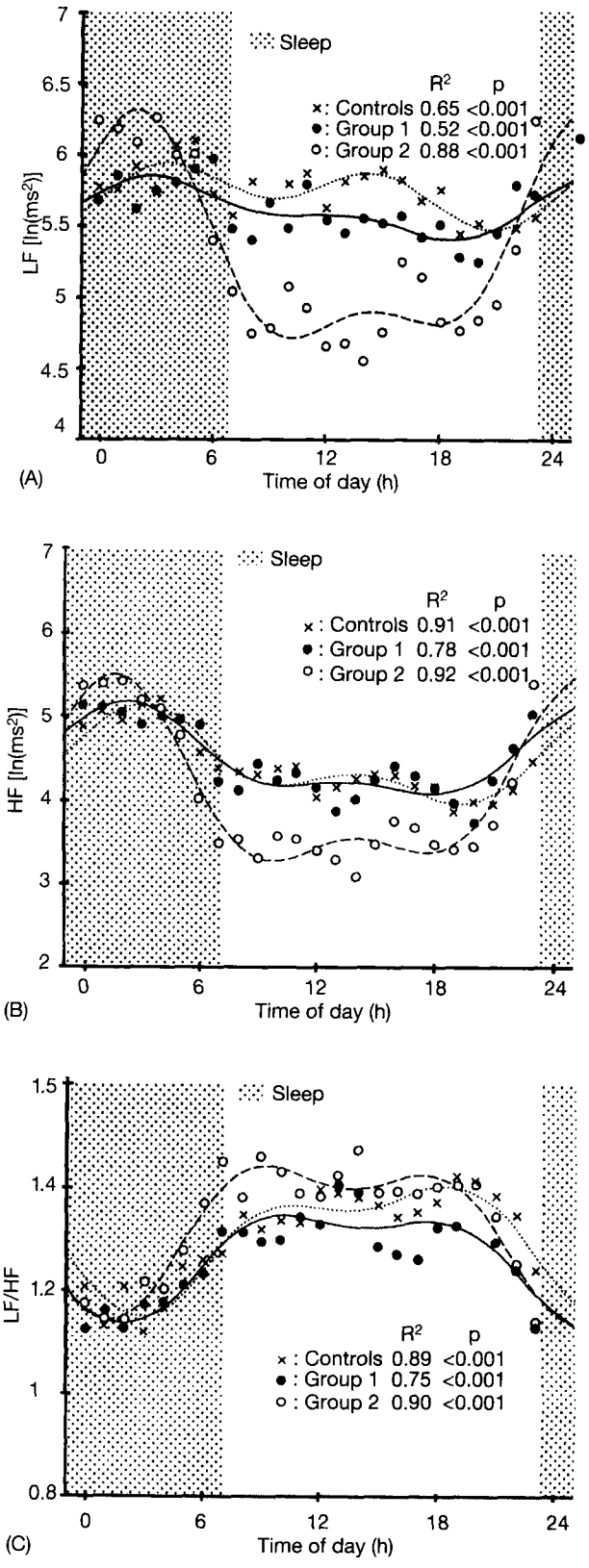


FIG. 1 Circadian rhythms in (A) low frequency (LF), (B) high frequency (HF), and (C) LF/HF. AI = apnea index, OSAS = obstructive sleep apnea syndrome, Group C = controls, Group 1 = mild OSAS (AI < 20), Group 2 = severe OSAS (AI ≥ 20).

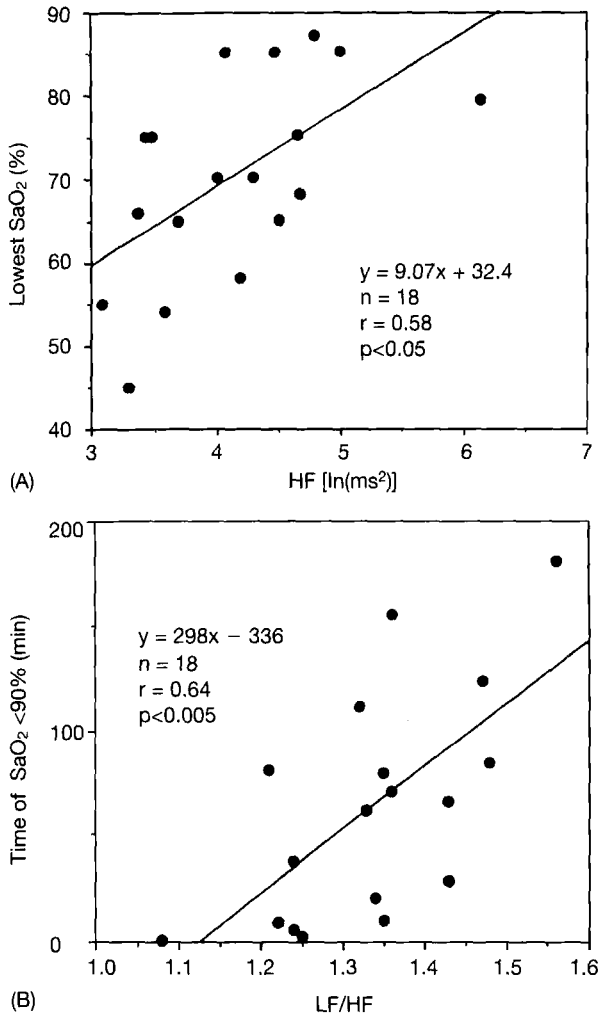


FIG. 2 (A) Correlation between the high frequency (HF) from 4 A.M. to 12 noon and lowest $SaO_2$ during sleep, and (B) correlation between ratio of low-to-high frequency power (LF/HF) from 4 A.M. to 12 noon and total time during which nocturnal oxygen saturation was < 90% (time of $SaO_2$ < 90%) in patients with obstructive sleep apnea syndrome.

ratio in Group 2 were significantly different from those in the control group or in Group 1 ($p < 0.05$) (Fig. 1). Neither hypertension nor LVH significantly influenced the circadian variation in the HF and LF/HF ratio.

The mean HF from 4 A.M. to 12 noon was significantly lower, and the mean LF/HF ratio during the same period was significantly higher in Group 2 than in the control group or in Group 1 (Table II). The mean HF and the mean LF/HF ratio from 4 A.M. to 12 noon correlated significantly with the lowest $SaO_2$ during sleep (HF: $r = 0.58$, $p < 0.05$, LF/HF ratio: $r = 0.56$, $p < 0.05$) (Fig. 2) (Table III). The mean LF/HF ratio correlated significantly with time of $SaO_2$ < 90% ($r = 0.64$, $p < 0.005$) (Fig. 2) (Table III).

Ventricular tachycardia was found in the early morning in one patient, sinus arrest in two patients, and ST depression in two patients in Group 2.

TABLE III Correlations between HF and LF/HF from 4 A.M. to 12 noon and polysomnographical variables

| | HF | LF/HF |
|---|---|---|
| No. of apneas | 0.42 | 0.35 |
| Apnea index | 0.44[c] | 0.37 |
| Lowest $SaO_2$ | 0.58[b] | 0.56[b] |
| Time of $SaO_2$ <90% | 0.41[c] | 0.64[a] |

[a] $p < 0.005$.
[b] $p < 0.05$.
[c] $p < 0.1$.
Data are correlation coefficients.
Abbreviations as in Table I.

## Discussion

The power spectral analysis of heart rate variability in the present investigation showed that (1) LF and HF were suppressed from early morning to daytime, and LF/HF ratio was elevated during sleep and daytime in patients with severe OSAS compared with patients with mild OSAS and control subjects, (2) neither hypertension nor LVH significantly influenced the circadian rhythm in heart rate variability in patients with OSAS. These findings suggest that OSAS per se may contribute to abnormal circadian rhythm of autonomic activity leading to the development of cardiovascular diseases.[29,30]

The heart rate changes cyclically in response to an apnea and a subsequent hyperventilation. The magnitude of the decrease in heart rate associated with the apneic episodes is related to the severity of oxygen desaturation,[14,15] and hypoxia resulting from the futile inspiratory efforts with an obstructed airway may activate the parasympathetic nervous system.[31–33] The reflex bradycardia, which is presumably mediated by the peripheral chemoreceptors and the vagi, is reversed by the pharmacologic vagal blockade.[11–13] The termination of obstructive apnea induces cortical arousal, which is usually associated with a marked decrease in the parasympathetic activity and an increase in heart rate.[33] In contrast, the sympathetic nervous system is activated by hypoxia, respiratory acidosis, and cortical arousal, all of which may contribute to an abrupt elevation in heart rate and blood pressure when the patency of upper airway is restored.[33–36] Thus, the transient hemodynamic changes have been observed at the termination of apnea and may be caused by the consequences of sleep-disordered breathing, such as cortical arousals, oxygen desaturation, swing in intrathoracic pressures, or increased sympathetic activity. However, the chronic effect of sleep-disordered breathing on the autonomic activity or cardiovascular system is not fully known.

Somers *et al.*[37] reported that the sympathetic activity in muscle and blood pressure during sleep were more elevated in patients with OSAS than in normal control subjects. The nocturnal concentration of plasma norepinephrine in patients with OSAS was increased and correlated with the severity

of overnight oxygen desaturation.[38] In the present investigation, LF and HF decreased from early morning to daytime, the LF/HF ratio which reflects sympathetic activity was increased particularly during nighttime and the first hours after awakening, and showed morning surge of the LF/HF ratio in patients with severe OSAS. It was proportional to the degree of the nocturnal oxygen desaturation. The circadian pattern of LF/HF ratio was consistent with the circadian variation in blood pressure, which was previously observed in patients with severe oxygen desaturation.[30] We also found that hypertension and LVH were more prevalent in patients with severe OSAS than in those with mild OSAS. The mechanisms of daytime hypertension in OSAS has not been clearly demonstrated. Our findings suggest that frequent episodes of hypoxia, respiratory acidosis, pleural pressure swings, arousal responses, and the resulting elevation in catecholamine secretion may contribute to an elevation in sympathetic activity, not only during nighttime but also during daytime.[36–40] Abnormal circadian rhythm of autonomic activity in patients with severe OSAS may lead to the development of daytime hypertension and LVH,[30,41] which may be supported by a report from a canine model of Brooks *et al.*[29]

The early morning dip in the HF in patients with severe OSAS, indicating the suppressed parasympathetic activity, may have been related to the severity of nocturnal oxygen desaturation. The poor prognosis for patients with severe OSAS may be related to the increased incidence of cardiovascular complications.[4–6] The abnormality in autonomic activity, which was indicated by decreased indices of heart rate variability, is related to an increase in the susceptibility to the ventricular arrhythmias, cardiac failure, diabetes, and risk factor for mortality post myocardial infarction.[14–16] Myocardial infarction, ischemia, and sudden cardiac death occur predominantly in the early morning.[23,25] Humoral vasoconstrictors, norepinephrine, plasma viscosity, platelet aggregability, and vascular resistance significantly increase in the morning.[24] REM sleep in the morning is related to ischemia, cardiac arrhythmia, and sudden cardiac death.[23–26] Therefore, the suppressed parasympathetic activity in the early morning to daytime, which was indicated by decreased HF in patients with severe OSAS in our study, might contribute to ischemic changes, cardiac arrhythmia leading to cardiovascular accident, and development and progression of the cardiovascular atherosclerotic diseases.[14,15,21] The imbalance between sympathetic and parasympathetic activity may be related to the high prevalence of cardiovascular disease in OSAS, not simply to reductions in vagal tone.

The HF disappears after the administration of atropine, suggesting that it may reflect vagal activity.[42] The possibility of providing an index of the sympathetic activity is less well established, although the ratio of LF to HF components has been used as an index of overall sympathovagal balance in normal subjects.[18] The LF component seems to correspond to Mayer waves.[43] Speculation about the origin of the LF component includes body temperature,[44] blood flow,[45] fluctuations in activity of the renin-angiotensin system,[18] baroreceptor reflexes,[46] and periodic breathing.[47,48] We cannot exclude the possibility that some, even if not all, parts of these components could arise from the sympathetic regulation. The specific frequency of heart rate variability mediated by periodic breathing is $< 0.04$ Hz.[47,48] The LF (0.04–0.15 Hz) was unlikely to be influenced by periodic breathing in the present study.

Spectral analysis of heart rate variability provides important information about the influence of sleep apnea on the circadian variation of autonomic activity. Our findings suggest that disturbed circadian rhythm of autonomic activity may increase the morbidity and mortality related to underlying cardiovascular atherosclerotic diseases.

## Acknowledgments

The authors thank Professor Clifford W. Zwillich, Dr. Yuhei Ichimaru, Dr. Masami Nagashima, and Dr. Goto Masahiko for their advice, and Mr. Norio Sugimoto for his help in the statistical analyses.

## References

1. Shepard JW: Hemodynamics in obstructive sleep apnea. In *Abnormalities of Respiration During Sleep* (Ed. Fletcher EC), p. 39–61. Philadelphia: Grune & Stratton, 1986
2. Strohl KP, Saunders NA, Sullivan CE: Sleep apnea syndrome. In *Sleep and Breathing* (Eds. Saunder NA, Sullivan CE), p. 365–402. New York: Marcel Dekker, 1984
3. Partinen M, Jamieson A, Guilleminault C: Long-term outcome for obstructive sleep apnea syndrome patients: Mortality. *Chest* 1988; 94:1200–1204
4. He J, Kryger MH, Zorick FJ, Conway W, Roth T: Mortality and apnea index in obstructive sleep apnea: Experience in 385 male patients. *Chest* 1988;94:9–14
5. Guilleminault C: Natural history, cardiac impact, and long-term follow-up of sleep apnea syndrome. In *Sleep/Wake Disorders: Natural History, Epidemiology, and Long-Term Evolution* (Eds. Guilleminault C, Lugaresi E), p. 107–125. New York: Raven Press, 1983
6. Peter JH: Sleep apnea and cardiovascular disease. In *Obstructive Sleep Apnea Syndrome: Clinical Research and Treatment* (Eds. Guilleminault C, Partinen M), p. 81–98. New York: Raven Press, 1990
7. Lugaresi E, Cirignotta F, Coccagna G, Piana C: Some epidemiological data on snoring and cardiocirculatory disturbances. *Sleep* 1980;3:221–224
8. Koskenvuo M, Kaprio J, Partinen M, Langinvainio H, Sarna S, Heikkila K: Snoring as a risk factor for hypertension and angina pectoris. *Lancet* 1985;1:893–896
9. Norton PG, Dunn EV: Snoring as a risk factor for disease: An epidemiological survey. *Br Med J* 1985;291:630–632
10. Partinen M, Palomaki H: Snoring and cerebral infarction. *Lancet* 1985;2:1325–1336
11. Tilkian AG, Guilleminault C, Schroeder JS, Lehrman KL, Simmons FB, Dement WC: Sleep induced apnea syndrome: Prevalence of cardiac arrhythmias and their reversal after tracheostomy. *Am J Med* 1977;63:348–358
12. Guilleminault C, Connolly S, Winkle R, Melvin K, Tilkian A: Cyclical variation of the heart rate in sleep apnoea syndrome. *Lancet* 1984;21:126–134
13. Zwillich C, Devlin T, White D, Douglas N, Weil J, Martin R: Bradycardia during sleep apnea: Characteristics and mechanism. *J Clin Invest* 1982;69:1286–1292

14. Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ, the Multicenter Post-Infarction Research Group: Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987;59:256–262
15. Martin GJ, Magid NM, Myers G, Barnett PS, Schaad JW, Weiss JS, Lesch M, Singer DH: Heart rate variability and sudden death secondary to coronary artery disease during ambulatory electrocardiographic monitoring. *Am J Cardiol* 1987;60:86–89
16. Indolfi C, Ross J: The role of heart rate in myocardial ischemia and infarction: Implications of myocardial perfusion-contraction matching. *Progr Cardiovasc Dis* 1993;36:61–74
17. Akselrod S, Gordon D, Ubel FA, Shannon DC, Barger AC, Cohen RJ: Power spectral analysis of heart rate fluctuation: A quantitative probe of beat to beat cardiovascular control. *Science* 1981;213: 220–222
18. Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, Sandrone G, Malefatto G, Gerutti S, Malliani A: Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circ Res* 1986;59:178–193
19. Hayano J, Sakakibara Y, Yamada M, Ohte N, Fujinami T, Yokoyama M, Wantanabe Y, Takata K: Decreased magnitude of heart rate spectral components in coronary artery disease. Its relation to angiographic severity. *Circulation* 1990;81:1217–1224
20. Chakko S, Mulingtapang RF, Huikuri HV, Kessler KM, Materson BJ, Myerburg RJ: Alterations in heart rate variability and its circadian rhythm in hypertensive patients with left ventricular hypertrophy free of coronary artery disease. *Am Heart J* 1993;126: 1364–1372
21. Bigger JT, Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN: Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation* 1992;85: 164–171
22. Vaishnav S, Stevenson R, Marchant B, Lagi K, Ranjadayalan K, Timmis AD: Relation between heart rate variability early after acute myocardial infarction and long-term mortality. *Am J Cardiol* 1994;73:653–657
23. Rocco MB, Barry J, Campbell S, Nabel E, Cook EF, Goldman L, Selwyn AP: Circadian variation of transient myocardial ischemia in patients with coronary artery disease. *Circulation* 1987;75: 395–400
24. Goseki Y, Matsubara T, Takahashi N, Takeuchi T, Ibukiyama C: Heart rate variability before the occurrence of silent myocardial ischemia during ambulatory monitoring. *Am J Cardiol* 1994;73: 845–949
25. Smolensky M, Halberg F, Sargent F: Chronobiology of the life sequence. In *Advances in Climatic Physiology* (Eds. Ito S, Ogata K, Yoshimura H), p. 281–318. Tokyo: Igaku Shoin, 1972
26. Nowlin J, Troyer W, Collins W, Silverman G, Nighols GR, McIntosh HD, Estes EH, Bogdonoff MD: The association of nocturnal angina pectoris with dreaming. *Ann Intern Med* 1965;63: 1040–1046
27. Guilleminault C, Tilkian A, Dement WC: The sleep apnea syndromes. *Ann Rev Med* 1976;27:465–484
28. Kanematsu K, Hayashi H, Hatano K, Yoshikane M, Tsuda M: A new statistical method for the evaluation of the circadian blood pressure variance. *Jpn Intern J* 1990;5:78–79
29. Brooks D, Horner RL, Kozar LF, Render-Teixeira CL, Phillipson EA: Obstructive sleep apnea as a cause of systemic hypertension. Evidence from a canine model. *J Clin Invest* 1997;99:106–109
30. Noda A, Okada T, Hayashi H, Yasuma F, Yokota M: 24-hour ambulatory blood pressure variability in obstructive sleep apnea syndrome. *Chest* 1993;103:1343–1347
31. Kato H, Menon AS, Slutsky AS: Mechanisms mediating the heart rate response to hypoxemia. *Circulation* 1988;77:407–414
32. Slutsky AS, Rebuck AS: Heart rate response to isocapnic hypoxia in conscious man. *Am J Physiol* 1978;234:H129–H132
33. Lin YC, Shida KK, Hong SK: Effects of hypercapnia, hypoxia, and rebreathing on heart rate response during apnea. *J Appl Physiol* 1983;54:166–171
34. Scharf SM: Influence of sleep and breathing on cardiovascular function. In *Sleep and Breathing* (Eds. Saunders NA, Sullivan EA), p. 221–239. New York: Marcel Dekker, 1984
35. Noda A, Okada T, Yasuma F, Hayashi H, Suzuki R, Yokota M, Ohta T, Takeuchi J: Heart rate variability in sleep apnea syndrome. *Kokyu to Junkan* 1990;38:1097–1105
36. Bradley TD, Phillipson EA: Pathogenesis and pathophysiology of the obstructive sleep apnea syndrome. *Med Clin N Am* 1985;69: 1169–1185
37. Somers VK, Dyken ME, Mark AL: Autonomic and hemodynamic responses during sleep in normal and sleep apneic humans. *Clin Res* 1991;39:735A
38. Ozaki N, Okada T, Iwata T, Ohta T, Kasahara Y, Kikuchi K: Plasma norepinephrine in sleep apnea syndrome. *Neuropsychobiology* 1986;16:88–92
39. Yasuma F, Kozar LF, Kimoff RJ, Bradley TD, Phillipson EA: Interaction of chemical and mechanical respiratory stimuli in the arousal response to hypoxia. *Am Rev Respir Dis* 1991;143:1274–1277
40. Phillipson EA, Sullivan CE, Read DJC, Murphy E, Kozar LF: Ventilatory and waking response to hypoxia in sleeping dogs. *J Appl Physiol* 1978;44:512–520
41. Noda A: Cardiac hypertrophy in obstructive sleep apnea syndrome. *Chest* 1995;107:1538–1544
42. Pomeranz B, Macaulay RJB, Caudill MA, Kutz I, Adam D, Gordon D, *et al.*: Assessment of autonomic function in humans by heart rate spectral analysis. *Am J Physiol* 1985;248:H151–H153
43. Penaz J: Mayer waves: History and methodology. *Autonomedica* 1978;2:135–141
44. Kitney RI: An analysis of the non-linear behavior of the human thermal vasomotor control system. *J Theor Biol* 1975;52:231–248
45. Golenhofen K, Hildebrandt G: Die Beziehungen des Blutdruckrhythmus and periphere Durchblutung. *Pflugers Arch* 1958;267: 27–45
46. Malliani A, Pagani M, Lombardi F: Methods for assessment of sympatho-vagal balance: Power spectral analysis. In *Vagal Control of the Heart: Experimental Basis and Clinical Implications* (Eds. Levy MN, Schwartz PJ), p. 433–454. New York: Futura Publishing Company, 1994
47. Ichimaru Y, Ichimaru M, Kodama Y, Yanaga T: Detection of periodic breathing during 24-hour ambulatory ECG monitoring. *Computer in Cardio* 1988;88:411–414
48. Ichimaru Y, Yanage T: Frequency characteristics of the heart rate variability produced by Cheyne-Stokes respiration during 24-hr ambulatory electrocardiographic monitoring. *Computers Biomed Res* 1989;22:225–233