J. Sleep Res. (1993) **2,** 88–90

Power spectrum analysis and heart rate variability in Stage 4 and REM sleep: evidence for state-specific changes in autonomic dominance

I. BERLAD, A. SHLITNER, S. BEN-HAIM and P. LAVIE
Sleep Laboratory and Department of Physiology, Technion, Israel Institute of Technology, Haifa, Israel

Accepted in revised form 7 April 1993; manuscript received 13 July 1992

SUMMARY The present study investigated autonomic activity during NREM and REM sleep stages and wakefulness by spectral analysis of heart rate variability. The results demonstrated that NREM sleep in humans was characterized by a widely different autonomic activation pattern than REM sleep: high parasympathetic activity was found in NREM, while REM was characterized by attenuated vagal tone, and augmented sympathetic activity. The overall pattern during wakefulness showed an intermediate position between NREM and REM patterns; parasympathetic activity was lower than in NREM and higher than in REM, with an opposite trend for sympathetic activity.

KEYWORDS autonomic dominance, heart rate, power spectrum, vagal tone.

INTRODUCTION

Early experiments investigating the function of the autonomic nervous system during sleep traditionally relied on invasive techniques. Baust *et al.* (1968), who chronically implanted electrodes in a cat in order to record sympathetic output, revealed no noticeable differences in activity between relaxed wakefulness and synchronized sleep (NREM sleep). A prominent reduction in sympathetic activity occurred, however, during desynchronized sleep (REM sleep). Different forms of heart denervation showed that the drop in heart rate occurring during the transition from wakefulness to NREM sleep was caused mainly by an increase in parasympathetic activity (Baust and Bohnert 1969). A further decrease during REM sleep was caused by a reduction of sympathetic activity, on which transient heart rate accelerations linked to phasic REM events were superimposed. Parmeggiani (1984) reported that in man not only did the heart rate not decrease during the shift from NREM to REM, it sometimes even showed a slight increase. This was explained by the preponderance of phasic REM events in man. Using intraneural recordings of multiunit sympathetic activity, Hornyak *et al.* (1991) reported that muscle sympathetic activity in humans decreased during NREM sleep and increased during REM. A preliminary report on a possible decrease in parasympathetic activation, and an increase in sympathetic activation in REM sleep was reported by Zemaityte *et al.* (1984). Raetz *et al.* (1991) examined state-dependent beat-to-beat changes in the heart rate of a cat by plotting each cardiac RR interval against the previous interval. They found an increased sympathetic influence combined with a withdrawal of vagal tone in wakefulness. NREM plots showed a pattern consistent with a dominant contribution of vagal influence, while REM displayed a combination of the awake and NREM profiles.

In the present study, we utilized a noninvasive technique based on spectral analysis of heart rate fluctuations (Akselrod *et al.* 1981; Pomeranz *et al.* 1986) to investigate autonomic dominance during REM, Stage 4 NREM and wakefulness in men. Heart rate fluctuations have been shown to reflect the functioning of the two branches of the heart control mechanisms: i.e. the parasympathetic and the sympathetic systems (Baust and Bohnert 1969; Akselrod *et al.* 1981; Pomeranz *et al.* 1985). Spectral analysis of heart rate variability (HRV) in conscious dogs and in man (Akselrod *et al.* 1981; Pomeranz *et al.* 1985; Pagani *et al.* 1986) revealed two or three main components: a high-frequency component (around 0.25 Hz), associated with the respiratory cycle and mediated solely by the parasympathetic division, and one or two low-frequency components (<0.12 Hz), which may be jointly mediated by

Correspondence: P. Lavie, PhD, Sleep Laboratory, Faculty of Medicine, Technion-Israel Institute of Technology, Haifa 32000, Israel. Fax: 972-4-323045.

the sympathetic and parasympathetic branches. We show that this method reveals robust state-specific differences in autonomic activation patterns.

METHOD

Twenty healthy volunteers, aged 18–46 years (mean age 29.2 ± 5.8 y) slept one night in the laboratory. All refrained from taking any medication for at least one week before the study. All were well adapted to the sleep laboratory environment. Polysomnographic recordings consisting of EEG ($C_z - O_z$ and $P_z - C_z$), EMG (submental), EOG (left and right canthi) and ECG (precordial surface electrodes) were recorded simultaneously on paper and on an eight-channel Teac RD-111T PCM tape recorder. Sleep stages were scored in 30-s epochs according to standard criteria (Rechtschaffen and Kales 1968). In each of the recordings, 5-min epochs of NREM sleep (stage 4 during the first and second sleep cycles), REM sleep (second and third periods of the night) and quiet wakefulness before sleep onset, were visually identified; ECG records obtained during these epochs were played back from the tape and digitized at 512 Hz into a Microvax computer. A specially designed program identified the peak of each electrocardiographic R-wave and created a file containing the time points of each peak (R list), which was then manually edited to eliminate inappropriate detections. Subsequently, the time series constructed from the differences between $R_n - R_{n-1}$ were analysed by spectral analysis. Because the sequence of $R - R$ intervals is not a time series, but a point process, the frequency of the spectrum was expressed in units equivalent to cycles/s ('EqHz'). It was calculated by dividing the number of R-peaks by the actual time length (Pagani *et al.* 1986). To compare the spectrum between the three different conditions, neighbouring frequency bins were combined to 20 equal-size frequency bands (each of 0.025 EqHz).

Then, the integrated spectrum values of each of the bands were compared between conditions by the Wilcoxon ranked pairs test. DC was eliminated before the spectral analysis by subtracting the mean.

RESULTS

Five-minute sections of ECG data from REM, stage 4 NREM sleep and wakefulness were available for all subjects. Figure 1a shows the power spectral functions of HRV for REM and Stage 4 averaged across all 20 subjects. The low-frequency peak (typically below 0.05 Hz) was 4–5 times higher in REM than in Stage 4 sleep. The opposite was found for the high-frequency peak (typically at 0.2–0.3 Hz); it was substantially higher in Stage 4 than in REM sleep. While the high-frequency peak was completely abolished in REM sleep, the low-frequency peak was attenuated but not abolished in Stage 4 sleep. The Wilcoxon test revealed significant differences in opposite directions for the low (0.025 EqHz) and the medium to high (0.1–0.32 EqHz) frequency ranges (indicated by bars in Fig. 1a).

Spectral analysis of the RR intervals during wakefulness showed a less consistent pattern. Significant differences were found for wider frequency ranges when wakefulness was compared to REM sleep (Fig. 1b), than when wakefulness and Stage 4 sleep were compared (Fig. 1c). The overall pattern during wakefulness showed an intermediate position between Stage 4 and REM patterns. High-frequency activity in wakefulness was lower than in Stage 4 and higher than in REM, and the opposite trend was evident for the low-frequency activity. At the medium frequency (about 0.1 EqHz) a significant increase could be observed in wakefulness in comparison with both Stage 4 and REM sleep stages (with $P < 0.01$, $P < 0.05$, respectively).

DISCUSSION

The present results demonstrate that REM sleep in humans is characterized by a widely different autonomic activation pattern than Stage 4 NREM sleep. Autonomic activity during REM showed attenuated vagal tone, as indicated by the abolition of the spectral peak at the fast respiratory frequencies, and, possibly, a REM-related augmented sympathetic activity. The augmented sympathetic activity was indicated by the peak at low frequency which was significantly higher in REM than in NREM and

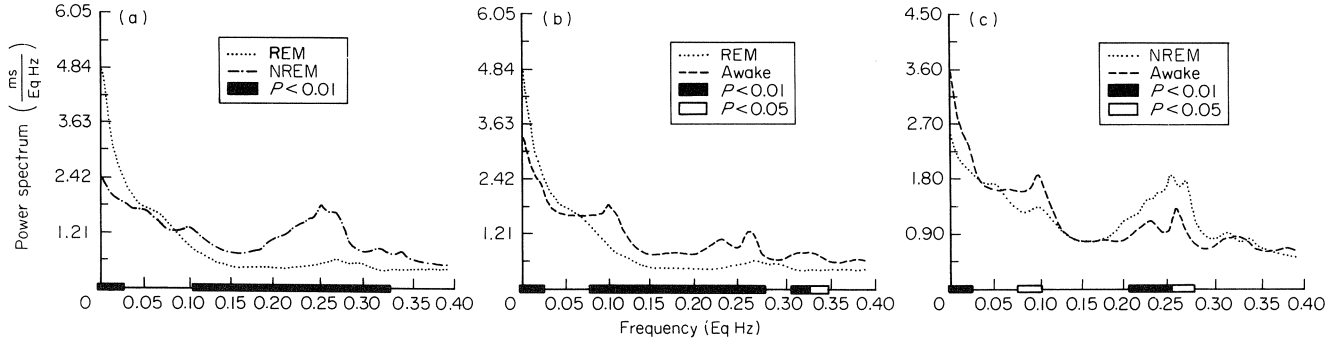

Figure 1. Comparison of mean power spectral density functions of ECG fluctuations in (a) REM sleep *vs* Stage 4 NREM sleep, (b) REM sleep *vs* awake, and (c) awake *vs* Stage 4 NREM sleep based on data from 20 subjects.

The bars indicate spectral zones for which there were statistically significant between-state differences (Wilcoxon paired test, white bar = at least $P < 0.05$, black bar = at least $P < 0.01$).

wakefulness. While the fast peak is solely contributed by the parasympathetic system, several processes might contribute to the augmentation of the low-frequency peak in REM sleep. First, it may indeed indicate REM-related sympathetic activation. This would corroborate previous data showing phasic REM-related increase in sympathetic activity (Zemaityte *et al.* 1984; Hornyak *et al.* 1991; Raetz *et al.* 1991). Second, other factors might contribute to the REM-related augmentation of the slow peak. It was shown that the amplitude of the low-frequency peak is also related to the activity of the renin–angiotensin system (Akselrod *et al.* 1981). Tonic activity of this system normally damps its amplitude, most probably via its influence on the peripheral tone. Blocking the renin–angiotensin system leads to a large increase in its magnitude. Since REM sleep was shown to be associated with a prominent decline in plasma renin activity (Brandenberger *et al.* 1988), it is possible that this contributes to the augmentation of the low-frequency peak. Furthermore, the fact that decreasing the activity of either the sympathetic or parasympathetic nervous systems by pharmacological means reduces the low-frequency peak, leaves open the possibility that REM sleep is associated with a joint activation of both systems. It should be mentioned, however, that a recent study conducted on SHR rats questioned the contribution of the sympathetic activity to the slow peak (Murphy *et al.* 1991). Possibly, the parasympathetic activation is mediated by non-vagal mechanisms, which may also mediate penile erections during REM sleep (Fisher *et al.* 1965).

The reverse pattern of activation was found for Stage 4 NREM sleep, an augmented vagal tone, as indicated by the prominent high-frequency peak, coincided with a considerable reduction of sympathetic activity, as indicated by the attenuation of the low-frequency peak. A decrease in sympathetic muscle activity during NREM sleep was previously demonstrated by interneural recordings (Hornyak *et al.* 1991). An increased vagal tone during NREM sleep was reported in other species as well (Baust and Bohnert 1969; Haddad *et al.* 1984).

The autonomic activation during wakefulness showed lower high-frequency, respiratory-mediated (parasympathetic) activity than in (Stage 4) NREM and higher than in REM, and an opposite trend for low-frequency activity, suggesting autonomic activity in opposite directions in NREM and REM sleep with respect to wakefulness. The findings emphasize the widely different patterns of autonomic activity during NREM and REM sleep stages. The medium-frequency peak (at about 0.1 EqHz) showed a significant increase in wakefulness when compared with both NREM and REM sleep. This medium frequency was reported to reflect the resonance frequency of the baroreflexes (Hyndman *et al.* 1971). Its augmentation during wakefulness might point to a different activation of the baroreflexes in sleep (both NREM and REM) as compared to wakefulness.

The present results, demonstrating robust differences in the pattern of autonomic activation in REM and NREM sleep, suggest that spectral analysis of HRV can be a convenient tool for the investigation of autonomic activity in sleep. Such investigations are particularly needed in view of recent reports linking sleep-specific autonomic activation with systemic hypertension and cardiovascular morbidity, such as in sleep apnoea syndrome (Furlan *et al.* 1990; Hedner *et al.* 1988).

REFERENCES

Akselrod, S., Gordon, D., Ubel, F. A. *et al.* Power spectrum analysis of heart rate fluctuations: A quantitative probe to beat-to-beat cadiovascular control. *Science,* 1981, 213: 220–222.

Baust, W. and Bohnert, B. The regulation of heart rate during sleep. *Exp. Brain Res.,* 1969, 7: 169–180.

Baust, W., Weidinger, H. and Kirchner, F. Sympathetic activity during natural sleep and arousal. *Arch. Ital. Biol.,* 1968, 106: 379–390.

Brandenberger, G., Follenius, M., Simon, C., Ehrhart, J. and Libert, L. P. Nocturnal oscillations in plasma Renin activity and REM-NREM cycles in humans: A common regulatory mechanism? *Sleep,* 1988, 11: 242–250.

Fisher, C., Gross, J. and Zuch, J. Cycle of penile erections synchronous with dreaming (REM) sleep. *Arch. Gen. Psych.,* 1965, 12: 29–45.

Furlan, R., Guzzetti, S., Crivellaro, W. *et al.* Continuous 24-hour assessment of the neural regulation of systemic arterial pressure and RR variabilities in ambulant subjects. *Circulation,* 1990, 81: 537–547.

Haddad, G. G., Jeng, H. J., Lee, S. H. and Lai, T. L. Rhythmic variations in R-R variabilities in ambulant subjects. *Am. J. Physiol.,* 1984, 247: H67–H73.

Hedner, J., Ejnell, H., Sellgren, J. *et al.* Is high and fluctuating muscle nerve sympathetic activity in the sleep apnoea syndrome of pathogenetic importance for the development of hypertension? *J. Hypertens.,* 1988, 6 Suppl. 4: S529–S531.

Hornyak, M., Cejnar, M., Elam, M., Matousek, M. and Wallin, G. Sympathetic muscle nerve activity during sleep in man. *Brain* 1991, 114: 1281–1295.

Hyndman, B. W., Kitney, R. I. and Sayers, B. McA. Spontaneous rhythms in physiologic control systems. *Nature Lond.,* 1971, 233: 339–341.

Murphy, C. A., Sloan, R. P. and Myers, M. M. Pharmacologic responses and spectral analyses of spontaneous fluctuations in heart rate and blood pressure in SHR rats. *J. Auton. Nerv. Syst.,* 1991, 36: 237–250.

Pagani, M., Lombardi, F., Guzzetti, S. *et al.* 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.

Parmeggiani, P. L. Autonomous nervous system in sleep. *Exp. Brain. Res.,* 1984, 54, Suppl. 8: 39–49.

Pomeranz, B., Macaulay, R. J. B., Caudill, M. A. *et al.* Assessment of autonomic function in humans by heart rate spectral analysis. *Am. J. Physiol.,* 1985, 248: H151–H153.

Raetz, S. L., Richard, C. A., Garfinkel, A. and Harper, R. M. Dynamic characteristics of cardiac R-R intervals during sleep and waking states. *Sleep,* 1991, 14: 526–533.

Rechtschaffen, A. and Kales, A. *A Manual of Standardized Terminology, Techniques and Scoring Systems for Sleep Stages of Human Subjects.* Brain Information Service/Brain Research Institute, Los Angeles, 1968.

Zemaityte, D., Varoneckas, G. and Sokolov, E. Heart rhythm control during sleep. *Psychophysiology,* 1984, 21: 279–289.