Heart rate variability and body temperature during the sleep onset period

Kazue OKAMOTO-MIZUNO,1,2 Yukari YAMASHIRO,1,3 Hideki TANAKA,4 Yoko KOMADA,1,5 Koh MIZUNO,1,6 Masako TAMAKI,7 Masako KITADO,6 Yuichi INOUE5 and Shuichi SHIRAKAWA1

1Department of Psychogeriatrics, National Institute of Mental Health, National Center of Neurology and Psychiatry, 2Tokyo Laboratories, Kao Corporation, 3Japan Somnology Center, Neuropsychiatric Research Institute, and 4Research and Development Center, Home Appliances Manufacturing, Business Unit, Matsushita Electric Works, Tokyo, 5Center for Welfare & Health Improvement and 6Faculty of Child and Family Studies, Tohoku Fukushi University, Miyagi, 7Department of Clinical Psychology, Faculty of Human and Social Environment and 2Department of Behavioral Sciences, Faculty of Integrated Arts and Sciences, Hiroshima International University, Hiroshima, Japan

Abstract
Heart rate variability (HRV) and body temperature during the sleep onset period was examined. The core body temperature and electrocardiogram were recorded continuously beginning 1 h before lights out (LO) until the end of the first rapid eye movement sleep (REM) in 14 young healthy subjects. HRV was calculated by the MemCalc method. The time course changes in body temperature and HRV was analyzed before and after sleep onset, and during the following eight consecutive phases: the 60 min before LO, the 30 min before LO, LO, first stage 2 (sleep onset), first slow wave sleep (SWS), stage 2 just before REM, start of REM, and end of REM. A clear decline was observed in the ratio of the low frequency (LF) to high frequency (HF) component of HRV (LF/HF), normalized LF (LF/(LF + HF)), and body temperature prior to sleep onset both in the time course of the sleep onset period and in the consecutive phases. The HF increased prior to sleep onset in the consecutive phases, while no clear increase was observed in the time course of sleep onset period. Changes in LF/LF + HF and LF/HF preceded SWS and REM. These results suggest the existence of a strong coupling between the cardiac autonomic nervous system and body temperature at the sleep onset period that may not be circadian effects. Furthermore, LF/(LF + HF) and LF/HF may possibly anticipate sleep and the onset of each sleep stage.

Key words: body temperature, heart rate variability, sleep onset.

INTRODUCTION
In humans, at the normal sleep onset period, core body temperature declines due to an underlying circadian rhythm and sleep-evoked effects.1 The core body temperature decline takes place before sleep onset, and this rapid decline increases the likelihood of sleep initiation.2 The peripheral skin temperature (Tsk) increases prior to core body temperature decline. This indicates the important role peripheral Tsk plays in mediating a decrease in core body temperature.3-6 In turn, increased peripheral heat loss and/or core temperature decline may facilitate the onset of sleep.7,8 Furthermore, since sleep itself has a minor effect on the decline in core body temperature after sleep onset,9 and an increase in Tsk is
observed at any circadian timing before sleep onset, a thermoregulatory change prior to sleep onset is related to sleep onset, rather than to sleep itself or to circadian effects. These changes in thermoregulatory processes are in part, innervated by the autonomic nervous system, since peripheral task is controlled by the activity of the sympathetic nervous system on vessels regulating skin blood flow. However, it remains unknown whether these thermoregulatory processes at sleep onset are associated with cardiac autonomic activity.

Cardiac autonomic activity differs from wakefulness to sleep. Previous studies confirm that parasympathetic activity is dominant during non-rapid eye movement sleep (NREM). On the other hand, parasympathetic activity decreases and sympathetic activity increases during rapid eye movement sleep (REM). However, these results are based on the cardiac autonomic activity of each sleep stage through the night, and only few studies have focused on the transition in cardiac autonomic activity at sleep onset. The cardiac autonomic activity at sleep onset indexed by the pre-ejection period (PEP) and respiratory sinus arrhythmia (RSA) reveals that there is no marked change in sympathovagal balance, and that the autonomic nervous system is not involved in the anticipation of sleep. On the other hand, cardiac autonomic activity at sleep onset indexed by spectral analysis of heart rate variability (HRV) indicates that sleep onset strongly affects the vagal dominance in the sympathovagal balance, which is indexed by the ratio of the low frequency (LF) to the high frequency (HF) component of HRV (LF/HF). This discrepancy may be largely due to the measuring method since PEP and the spectral analysis of HRV show different results. Furthermore, in these previous studies, cardiac autonomic activity was not measured precisely at the transition from wakefulness just before lights out (LO) to sleep onset and in relation with changes in core body temperature.

The aim of this study was to examine the cardiac autonomic activity indexed by HRV that is a reliable non-invasive measurement of cardiac autonomic response and body temperature at the sleep onset period.

MATERIALS AND METHODS

Fourteen young healthy volunteers (n = 11, f = 3), with a mean age of 23.7 ± 4.7 years and a normal body mass index (over 18 under 24) served as subjects. They were informed about the protocol and provided written consent prior to the experiment. The subjects had no history or evidence of cardiovascular or respiratory disease. Their alcohol intake was limited to 350 mL per day for 1 week prior to the study and was not allowed during the study period. Smoking was not allowed from 1 week prior to the study to the end of the study period. Psychological tests and a questionnaire on sleep were administered prior to the experiment; the results showed that the subjects were physically and mentally healthy. The subjects were required to sleep and wake on a regular schedule and to maintain a sleep log from 1 week prior to the study to the end of the study period. Wrist actigraphy recordings were performed continuously from 1 week prior to the study to the end of the entire study period. All subjects adhered to a regular sleep–wake schedule. The actigraphy data did not suggest any evidence of napping, and none of the subjects reported a habit of taking naps.

The experiment was carried out in a chamber where the ambient temperature and relative humidity (RH) was maintained at 24 ± 1°C and RH60 ± 10%, respectively. The light was controlled at 30 lux throughout the experimental period. Before sleep, the subjects rested for 3 h to exclude any prior behavioral effects on sleep. Electrodes were attached to the subjects while they rested in a chair by the side of the bed. After this accumulation period, the subjects retired to the bed 10 min before their usual bed time and were asked to sleep until their usual wake-up time. To control circadian effects on sleep, bed times and waking times in the experiment were determined based on each subject’s actigraphy data, sleep log, and self-reported information. The subjects slept on a bed, which was covered with a bed sheet and a blanket, and wore their own pajamas. The subjects slept two nights, with the first night considered an adaptation night. Polysomnographic recordings, electrocardiogram (EGG), and rectal temperature (Trec) were measured continuously. Trec was continually measured by a thermistor probe (LTBA, Gram Co., Saitama, Japan) which was inserted 12 cm into the anus, at the time interval of 1 min. The electroencephalogram (EEG; C3-A2, C4-A1, O1-A2), electrooculogram (EOG), mental electromyogram (EMG), and ECG were recorded using a digital polygraph recorder (AP1000, TEAC Co., Tokyo, Japan). The EEG, EOG, EMG, and ECG signals were digitized at a sampling rate of 500 Hz. Sleep recordings were blind scored visually every 20 s based on the standard manual of Rechtschaffen and Kales, and the supplements and amendments criteria of the Japanese Society of Sleep Research.

The Holter ECG recordings were conducted and the recorded analog ECG signals were transformed to digital
signals for calculating the R-R intervals with a sampling rate of 500 Hz. After the ECG R-R intervals data were visually inspected for rejecting artifacts, power spectrum analysis of HRV was performed at 1-min intervals by an authorized MemCalc method with commercialized software (HrvCalc, Suwa Trust, Tokyo, Japan). This method is a combination of the maximum entropy method for spectral analysis and the non-linear least squares method for fitting analysis. HF (HF; 0.15–0.40 Hz), the ratio of LF (LF; 0.04–0.15 Hz) to HF (LF/HF), and normalized LF (LF/(LF + HF)) were analyzed. The T3e, HF, LF/HF, and LF/(LF + HF) at 60 min before lights out (LO) (–60), 30 min before LO (–30), at LO (GN), at sleep onset, the start of sleep stages 3 and 4 (SWS), S2 immediately before REM (S2R), the start of REM (REM1), and the end of REM (REM2) were analyzed to compare the differences in sleep stages. The effect of the time course of the sleep onset period on T3e, HF, LF/HF, and LF/(LF + HF) was analyzed from 60 min before sleep onset to 120 min after sleep onset at 5-min intervals. The time course of HRV and body temperature 60 min before LO to 120 min after LO was also analyzed to clarify the difference between sleep onset.

To test the statistical significance of the data, one-way analysis of variance (ANOVA) was used to analyze the effect of time on T3e, HF, LF/HF, and LF/(LF + HF). Fisher's protected least significant difference (PLSD) test was applied for the post-hoc pairwise comparison of T3e. The Wilcoxon test was used to further compare HF, LF/HF, and LF/(LF + HF). To analyze the correlation between T3e and HRV, Pearson's correlation matrix was used. The T3e and HRV changed 30 min prior to sleep onset and 35–60 min after sleep onset was analyzed.

RESULTS

The results of the sleep parameters during the experimental night are shown in Table 1. The sleep efficiency index and sleep stage distribution were in the normal range.²³ The time from LO to the start of stage 2 was scored as sleep latency, and this was in the normal range. The onset latency of SWS and REM was also in normal range.

<table>
<thead>
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<th>Table 1 Percentage of sleep stages during the experimental night</th>
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<td>Latency of (min)</td>
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Data are presented as mean ± SE. Percentages were calculated as a proportion of sleep onset to final morning walking. MT, moving time; REM, rapid eye movement; SFI, Sleep efficiency index. WASO, wake after sleep onset.

The greatest decrease during the 30-min period before LO to sleep onset. The LF/(LF + HF) and LF/HF clearly increased at stage 2 before REM and maintained an increased level until the end of the REM period. The HF gradually increased beginning from 60 min before LO to sleep onset. Although the HF tended to decrease until the end of the REM period, no significant difference was observed after sleep onset.

In order to observe the effect of the time course of sleep on HF, LF/HF, LF/(LF + HF), and T3e, changes in these parameters at 60 min before and 120 min after sleep onset were averaged every 5 min. The T3e (F2,28 = 3.33, P < 0.0001), HF (F2,28 = 1.50, P < 0.05), LF/HF (F2,28 = 1.40, P < 0.0001), and LF/(LF + HF) (F2,28 = 8.05, P < 0.0001) significantly changed depending on the time course of the sleep (Fig. 2). The T3e gradually began to decrease at 60 min before sleep onset; however, there was no significant difference after sleep onset. The LF/HF clearly began to decrease at 30 min before sleep onset and showed a minimum value at sleep onset. No significant decrease was observed in LF/HF after sleep onset. The LF/(LF + HF) clearly began to decrease at 30 min before sleep onset and further decreased approximately 20 min after sleep onset. The HF significantly began to increase at 10 min before sleep onset with a maximum increase at sleep onset. At 85–120 min after sleep onset, the HF significantly decreased as compared to its value at sleep
Figure 1. *P < 0.05 Heart rate variability and body temperature before sleep onset and at the onset of each sleep stage. HF, high frequency; LF, low frequency; GN, lights out; S2, start of stage 2; SWS, start of slow wave sleep; SR2, stage 2 immediately before REM; R1, start of REM; R2, end of REM.

onset. The changes in heart rate variability and body temperature at 60 min before and after LO were averaged every 5 min (Fig. 3). The Tre (F_{12,34} = 3.82, P < 0.0001), HF (F_{12,34} = 2.18, P < 0.0002), LF/HF (F_{12,34} = 15.92, P < 0.0001), and LF/(LF + HF) (F_{12,34} = 16.79, P < 0.0001) significantly changed depending on time. The Tre significantly decreased at LO as compared to 50–60 min before LO, and 60–70 min after LO. In HF, a significant difference between LO was observed between 50 and 60 min before LO, with no significant difference after LO. The

Figure 2. *P < 0.05 Time course of heart rate variability and body temperature during sleep onset period. HF, high frequency; LF, low frequency; 0, sleep onset.
LF (LF + HF) and LF/HF significantly decreased at LO as compared to the 60-min period before LO. The LF (LF/(LF + HF)) and LF/HF further decreased after lights off with a significant decrease between LO and 10–40 min after LO.

To observe the significant correlation between TR and HRV, correlation matrix was analyzed. The TR and HRV change 30 min prior to sleep onset and 35–60 min after sleep onset was analyzed separately. A significant correlation was observed between TR and LF/HF change prior to sleep onset (P < 0.05), while LF/(LF + HF) showed a strong tendency (P < 0.07). No significant correlation was observed between TR and LF/HF or LF/(LF + HF) changes after sleep onset. No significant correlation was observed between TR and HF changes prior to sleep onset and after sleep onset.

Since LF/(LF + HF) showed a clear change prior to sleep onset, the regression curve between time prior to sleep onset and LF/(LF + HF) were calculated using KaleidaGraph (ver. 4; Synergy Software, Reading, PA, USA) (Fig. 4). A significant correlation was observed between 30 min prior to sleep onset (P < 0.0001), 60 min prior sleep onset (P < 0.0001), and LF/(LF + HF), while no significant correlation was observed between 35 min to 60 min prior to sleep onset and LF/(LF + HF). A third regression curve between 60 min before sleep onset and LF/(LF + HF) is also shown in Figure 4. The regression curve for LF/HF showed the same result as LF/(LF + HF). No significant correlation was observed between 30 min prior to sleep onset, 60 min prior sleep onset, 35 min to 60 min prior to sleep onset, and HF.

Figure 4 Regression analysis between time prior to sleep onset and LF/(LF + HF). The asterisk indicates the significant correlation P < 0.05. HF, high frequency; LF, low frequency.
DISCUSSION

The most notable finding in this study was that body temperature and HRV clearly changed prior to sleep onset with minor circadian effects. With regard to HRV, LF/(LF + HF) and LF/HF decreased abruptly before sleep onset, regardless of the sleep stages and time course of the sleep, while HF increased gradually. This result indicates the existence of an association between core body temperature and HRV at the sleep onset period.

The thermoregulatory process is directly involved in the facilitation of normal sleep onset. The core body temperature declines prior to sleep onset, and a rapid and steep decline increases the likelihood of sleep initiation. An increased peripheral Tsk mediates this process, allowing greater heat loss to the environment through the skin surface. The elevation of Tsk is largely due to increased skin blood flow that is regulated primarily through two pathways in the sympathetic nervous system: the noradrenergic vasoconstrictor system and the active vasodilator system. The increased skin temperature at sleep onset is attributable primarily to the reduced activation of noradrenergic vasoconstrictor tone in the skin sympathetic nervous activity (SSNA). The human thermoregulatory function is largely dependent on SSNA, that is suppressed during NREM sleep. It has been demonstrated that there is a pathway between the central autonomic network that controls cardiovascular responses and the activity of the neurons modulated by neurotransmitters acting as sleep promotion or sleep–wake transition factors. It is possible that SSNA prior to sleep onset is also linked with this pathway, and in turn, body temperature. Interestingly, LF/(LF + HF) and LF/HF showed a strong association with body temperature with an abrupt decrease at 30 min prior to sleep onset. This is supported by the fact that there was a significant correlation between Tre and LF/HF decrease at sleep onset (P < 0.01) and a strong tendency between Tre and LF/(LF + HF) (P < 0.07), while there was no significant correlation between Tre and HF. Furthermore, changes in Tre and HRV changes after sleep onset did not show any significant correlation. The results of the HRV and body temperature before and after LO further support this notion. A significant decrease in Tre at LO was observed only between 50 and 60 min before and 60–70 min after LO. The LF/HF and LF/(LF + HF) at LO significantly decreased as compared to the 60-min period before LO, and further decreased at 10–40 min after LO. Although further studies on manoeuvres that disturb sleep onset after lights off are needed, the relation between body temperature and HRV does not follow the same change at LO and sleep onset, indicating that it is not lights off, but rather sleep onset, that leads to the strong association between body temperature and HRV.

LF/HF and LF/(LF + HF) are widely interpreted as an index of sympathovagal balance. However, a number of studies have indicated that LF/HF and LF/(LF + HF) cannot be taken as accurate measurements of sympathovagal balance. The HRV results in our study should be interpreted with caution with regard to cardiac autonomic activity. However, the abrupt decrease in LF/HF and/or LF/(LF + HF) at sleep onset was in agreement with the results of a previous study. A strong inverse coupling between oscillations in slow wave activity and LF/HF or LF/(LF + HF) has been demonstrated. The delta EEG and spectral analysis of EEG correlate highly with LF/(LF + HF) and LF/HF, with no correlation between HF. Furthermore, changes were observed in LF/HF and/or LF/(LF + HF) prior to EEG changes. Taken together, our results may possibly suggest the strong involvement of body temperature and sympathovagal balance in facilitating sleep onset. This also supports the proposal that in a good sleeper, an oscillatory process that anticipates sleep may exist in sympathovagal balance and underlies the cardiovascular and thermoregulatory responses at sleep onset. Furthermore, considering that cardiac autonomic activity at sleep onset indexed by the PEP reveals that there is no marked change in sympathovagal balance, HRV may be a good indicator for detecting sympathovagal balance at the sleep onset period. Changes in sympathovagal balance were most likely attributable to a decreased LF, since HF increased gradually with a weak change in the time course of sleep onset. LF is related with predominant sympathetic changes. However, this interpretation is controversial, since it is generally accepted that both sympathetic and parasympathetic activity is contained. Regarding LF/HF or LF/(LF + HF) as parameters of sympathetic nervous activity has been questioned. However, the decrease in the cardiac sympathetic tone is the major determinant of cardioeculatory changes observed in NREM. The LF/(LF + HF) and cardiac sympathetic activity indexed by the PEP decrease during sleep. The LF and HF are oscillatory components of SSNA, which is similar to the corresponding components of muscle sympathetic nervous activity (MSNA),
and are coherent with oscillations in the R-R interval. These oscillatory patterns in SSNA possibly reflect common central mechanisms regulating sympathetic outflows subserving in different regions and functions, and contribute to a functional interaction between cardiovascular and thermoregulatory responses. Hence, a strong association between body temperature and LF/LF+HF, and LF/HF may indicate the indisputable involvement of sympathetic nervous activity in facilitating sleep onset.

Another interesting finding was that no significant change was observed in body temperature after sleep onset, while LF/LF+HF and LF/HF changed prior to SWS and REM. The changes in body temperature were in agreement with those observed in a previous study. This indicates that sleep itself has a minor effect on the decline in core body temperature after sleep onset. Furthermore, since an increase in Tsk is observed at any circadian time before sleep onset, a thermoregulatory change prior to sleep onset is related to sleep onset itself rather than to sleep or circadian effects. On the other hand, the changes in LF/LF+HF and LF/HF prior to SWS and REM were in agreement with those observed in previous studies. The variations in HRV are dependent on sleep onset and sleep-stages and are influenced only to a slight extent by the circadian clock. The results of the regression curve of LF/LF+HF further support this notion. A significant correlation was observed between 30 min prior to sleep onset and LF/LF+HF, while no significant correlation was observed in the 35-60 min period prior to sleep onset. The sudden decline in LF/LF+HF at 30 min prior to sleep onset is difficult to explain when only taking the circadian effect into account, and suggest that these changes are more probably sleep-onset specific. It is most probable that sympathovagal balance starts to change from 30 min prior to sleep onset, which is earlier than the skin potential resistance change reported by Niimi. These results indicate that the strong association between body temperature and HRV is limited to the 30-min period prior to sleep onset that may be sleep-onset specific. Although further studies on body temperature and HRV in manoeuvres that disturb sleep onset are needed, our results indicate that the body temperature and cardiac autonomic process prior to sleep onset may play a crucial role in initiating normal sleep onset. The changes in LF/LF+HF and LF/HF prior to SWS and REM may be due to the insensitivity of the standard sleep scoring. However, HRV changes that precede those observed in the EEG are indicative that the insensitivity of the scoring may not be the sole reason. Changes in the LF/LF+HF and LF/HF prior to shifts in the sleep stage suggest that these parameters are important in anticipating and maintaining each sleep stage; this finding supports the results of a previous study.

In conclusion, changes in the cardiac autonomic nervous system precede sleep onset, which is strongly associated with changes in body temperature. Furthermore, changes in LF/LF+HF and LF/HF precede sleep onset, SWS, and REM. This indicates that cardiac autonomic activity may possibly anticipate onset of sleep, SWS, and REM.

REFERENCES


