The Relationship Between Slow-wave Activity, Body Temperature, and Cardiac Activity During Nighttime Sleep

Helen J. Burgess PhD, Alexandra L. Holmes BSc (Hons), and Drew Dawson PhD

Centre for Sleep Research, Queen Elizabeth Hospital, University of South Australia

INTRODUCTION

CARDIAC AUTONOMIC TONE DURING SLEEP IS MOST VALIDLY ASSESSED IN HUMANS VIA NONINVASIVE MEASUREMENT TECHNIQUES: typically spectral analysis of the electrocardiogram signal. Use of these techniques has produced findings that suggest that cardiac parasympathetic (vagal) tone increases from wake to NREM sleep (often increasing progressively across the four NREM stages) and decreases from NREM to REM sleep (e.g., 1-3). Conversely, cardiac sympathetic activity has been reported to show the opposite changes to those observed in parasympathetic activity (e.g., 1-3). However, these studies all examined discrete blocks of data selected from nighttime sleep and often did not report the time of night from which the data were selected. Thus, these reports of apparent changes in cardiac autonomic tone across sleep stages may well be confounded by underlying circadian mediated alterations in cardiac autonomic tone.

More recent work has examined potential circadian influences on cardiac autonomic activity via use of the constant routine4-5 and forced desynchrony protocols.6 The results from this body of work suggest that the respective tonic levels of the two nervous systems controlling cardiac activity are differentially influenced by sleep and the circadian system and, as a result, do not alter reciprocally but instead have different time courses. Specifically, cardiac parasympathetic activity is predominantly influenced by the circadian system, such that it increases prior to sleep onset, while cardiac sympathetic activity is mainly influenced by sleep and decreases significantly after sleep onset.

More detailed work is required to further examine the specific influence of sleep on cardiac sympathetic activity. To date, only one study has investigated the pattern of change in cardiac sympathetic activity across entire nighttime sleep episodes, while controlling for sleep stage, and this study only examined Stage 2 NREM sleep.7 Furthermore, no study has examined alterations in cardiac sympathetic activity across consecutive NREM/REM sleep cycles. Therefore, there were two aims of the current study. The first was to examine the relationship between slow-wave activity (SWA, 0.33-3 Hz), a well recognized measure of NREM sleep intensity, and heart rate (HR), and the most strongly validated estimate of cardiac sympathetic activity (pre-ejection period, PEP) during NREM/REM sleep cycles. The second aim was to form a more complete picture of the pattern of change in sympathetic tone across NREM/REM sleep cycles by examining the relationships between the cardiac variables and core and peripheral body temperatures.

METHODS

Subjects

Ten healthy individuals (5 m, 5 f), with a mean age of 23.2±2.0 years and average body mass index (23.4±2.9 kg/m²) participated. Subjects were non-smokers and had no personal or family history of cardiovascular or respiratory disease. The subjects did not regularly consume large amounts of caffeine (< 350 mg/day) or alcohol (≤5 standard drinks/week), and participated in a moderate amount of exercise (≤10 hours per week). They were not taking any medication (currently or in the past week),
except that all of the females were taking an oral contraceptive (mono or multiphasic). Subjects had not undertaken any shift work or transmeridian travel in the past three months and had no history of sleep problems. They were not experiencing any major life stress and had no examinations scheduled for a few days before, during, or after the study.

The laboratory procedures were approved by The Queen Elizabeth Hospital Human Research Ethics Committee and the University of South Australia Human Research Ethics Committee. All subjects gave written informed consent prior to their participation and the experiment conformed to the Declaration of Helsinki. Subjects received financial reimbursement for their time.

Design

All experimental sessions were conducted at The Centre for Sleep Research at The Queen Elizabeth Hospital. Participants abstained from alcohol, caffeine, and other stimulants for 24 hours before and during the study. Participants were requested to maintain a self-selected constant sleep-wake schedule for one week prior to the experiment (verified by self-administered sleep-wake diaries and actigraph recordings). Participants attended the laboratory for at least one adaptation night prior to their single experimental night prior to participating in pairs.

Procedures

General laboratory procedures: In each session participants arrived at the Centre approximately two hours prior to their normal sleep onset time (23:00–00:30 hrs). Subjects toileted, had the equipment attached (see below), and were put to bed in individual bedrooms. All subjects kept their feet under the bed linen throughout the night. At their normal sleep onset time the lights were turned out and subjects were permitted to sleep. All subjects were left undisturbed until their normal wake time, at which time they were awakened and provided with a light breakfast. Ambient temperature of the bedrooms was maintained at 22°C±1°C.

Assessment of sleep-wake state: Each subject’s sleep-wake state was assessed by a central (C3-A2) and occipital (O1-A2) electroencephalogram (EEG) and an electro-oculogram (EOG; left and right outer canthi displaced vertically) according to standardized criteria.8 Electrodes were connected to a Medilog MPA-2 sleep analysis system (Oxford Medical Limited, Oxton, England). SWA (0.33–3 Hz) was assessed for each 30-second epoch, with a period amplitude analysis of the central EEG signal. Reliability and validity of the VU-AMS device is described elsewhere.12–13

Assessment of cardiac activity: An electrocardiogram (ECG) was obtained from disposable pregelled Ag/AgCl ECG spot electrodes (Meditrace, USA) that were placed at the jugular notch of the sternum, 4 cm under the left nipple and the right lateral side (ground). The electrodes were connected to a VU-AMS device (version 4.6, TD-FPP, Vrije Universiteit, Amsterdam, The Netherlands). The ECG was recorded by the VU-AMS device using an amplifier with a time constant of 0.3 seconds and 1 MOhm impedance and a low pass software filter of 17 Hz. Each R-peak was detected with a level detector with automatic level adjustment.10 From the R-peak time series, an average value for heart rate was obtained for each 30 seconds.

The VU-AMS also determined pre-ejection period (PEP) via impedance cardiography. PEP is the most strongly validated and reliable non-invasive measure of cardiac β-adrenergic sympathetic activity.11 PEP approximates the isovolumetric contraction time of the left ventricle—as cardiac sympathetic activity increases, PEP shortens. In order to measure PEP, a 350µA current at 50 KHz was passed through the body via “current” electrodes on the base of the neck over vertebrae C3/C4 and on the back over vertebrae T8/T9. Two “recording” electrodes, on the jugular notch and xiphoid process of the sternum, measured the resulting impedance (Z0), from which the change in impedance with time (dZ/dt) was derived. The dZ/dt signal was sampled at 250 Hz, and time locked to the R-wave to enable 30-second ensemble averaging of the dZ/dt signal. Thus for each 30-second period, PEP was later determined off-line as the time period between the R-wave on the ECG signal and the upstroke on the ensemble averaged dZ/dt signal. Reliability and validity of the VU-AMS device is described elsewhere.12–13

Assessment of body temperature: Rectal temperature was recorded using indwelling rectal thermistors (Steri-Probe 491B, Cincinnati Sub-Zero Products, Ohio, USA), self-inserted by the participants to 10 cm. Peripheral temperature was measured using thermistors (Steri-Probe 499B, Cincinnati Sub-Zero Products, Ohio, USA) attached to the arches of the soles of both feet. Thermistors were connected by cable to a 486 computer and the data was analyzed at a later date using a purpose-built temperature system (Strawberry Tree, California, USA). All temperatures were recorded at 30-second intervals with a sensitivity of 0.05°C.

Data Analysis

Data from sleep onset (first of three consecutive 30-second epochs of scored sleep) to final awakening was analysed. Thirty-second epochs of all the data were individually inspected and epochs that contained movement artifact were discarded. The temperatures from both feet were averaged to yield a mean foot temperature. As baseline cardiac activity and temperature vary widely between individuals, the variables for each subject were recalculated relative to each individual subject’s overall sleep period average, and these deviations from the mean were then averaged across the group. The group’s mean for each variable was then added to the data.

For the NREM-REM cycle analysis, the first three NREM-REM cycles from each subject were examined. The NREM-REM cycles were determined according to previously published criteria,14 with the exception that REM periods (apart from the first) were required to be at least three minutes in duration. Each subject’s NREM period was divided into 20 equal parts and each REM period was divided into four equal parts. In this way, each subject contributed different numbers of 30-second epochs to each bin, permitting the averaging of the changes in NREM-REM cycles across all subjects. This method was chosen as it is used widely when representing mean changes in SWA across NREM-REM cycles (e.g.,15–16).

Immediate changes in the dependent variables were also calculated at the specific NREM-REM transition points.
Assessed in two ways. The first compared the mean of each NREM episode with the mean of the subsequent REM episode with a paired t-test. In this case, statistical significance was determined at p<0.025. The second method examined the NREM-REM sleep transitions and each was analyzed with a one-way ANOVA. Here, statistical significance was determined at p<0.05, and the p-values were based on the Huynh-Feldt corrected degrees of freedom, but the original degrees of freedom are reported.

To investigate the relationships between SWA, cardiac activity, and temperature, Pearson product moment correlations were calculated for each individual, and group average correlations were determined using Fisher z-transformations. This was planned for the first three NREM-REM cycles of the sleep phase. To estimate the statistical significance of these correlations, a t-test was conducted to determine if the mean correlation was significantly different from zero. When interpreting these average correlations, more importance was attributed to the magnitude than the significance.

RESULTS

All subjects slept well with a high sleep efficiency (mean±SE; 92.19±1.34%) and normal sleep stage distribution (see Table 1). Furthermore, the average sleep onset latency to Stage 1 NREM sleep (time from lights out to start of first of three consecutive 30-second epochs scored as sleep) was within the normal range (7.26±1.26 mins). Due to technical problems, foot temperature recordings were lost from one subject. All variables were normally distributed.

As outlined above, three separate analyses were conducted and are reported below in this order. First, the variables were averaged in hourly bins and curve fits were made. Second, the variables were sorted from three minutes prior to three minutes after a transition between NREM and REM sleep and were analyzed with a one-way ANOVA. Third, correlations between the variables were calculated and averaged into a group mean.

Across-the-Night Analyses

As expected, in the first six hours of sleep, SWA significantly and linearly decreased across the night (F(1,9)=70.98, p=0.001; Fig.1). Rectal temperature decreased from the first to the second hour, increased to peak at the fourth hour and then slightly decreased to the sixth hour (Fig. 2). It was significantly fit with a cubic curve (F(1,9)=6.84, p=0.03). Foot temperature increased until the third hour, after which the temperature reached a plateau (Fig 2). It was significantly fit with a quadratic function (F(1,8)=14.26, p=0.005). HR increased from the first to second hour and then decreased to the fourth hour before it reached a plateau (Fig. 1). A cubic function was the most significant fit (F(1,9)=6.00, p=0.037). PEP significantly increased linearly across the night (F(1,9)=21.80, p=0.001; Fig 1).

NREM-REM Cycles

Mean SWA decreased from NREM to REM sleep in all cycles (cycle 1, p<0.001; cycle 2, p<0.001; cycle 3, p=0.002; see Fig. 1). Mean HR and PEP did not differ between NREM and the subsequent REM sleep period in all cycles (all p>0.05, see Fig. 1).
Figure 2—The average time course of rectal and foot temperature (degrees Celsius) during the first 3 NREM/REM sleep cycles. The center line represents the mean for 10 young healthy subjects for rectal temperature and 9 healthy subjects for foot temperature. The upper and lower lines represent ±1 SEM. The dark bottom bars represent REM sleep. The asterisks indicate where the mean for 10 young healthy subjects for rectal temperature and 9 healthy subjects for foot temperature were significantly different to the mean of the subsequent REM period (p<0.025). The average time from sleep onset of the NREM/REM period was significantly different to the mean of the subsequent REM period (p<0.05).

Figure 3—The average time course of slow-wave activity (µV/sec, 0.33-3 Hz), heart rate (beats/min) and pre-ejection period (msec) from 3 minutes before to 3 minutes after the first 3 NREM-REM and 2 REM-NREM sleep transitions. These transitions are represented by N-R and R-N respectively. The center line represents the mean for 10 young healthy subjects, and the upper and lower lines ± 1 SEM. The asterisks indicate where the change during the transition was significant (p<0.05).

Table 2—Mean Pearson product moment correlations between slow-wave activity and the remaining variables during the first three NREM-REM cycles of the sleep phase

<table>
<thead>
<tr>
<th></th>
<th>SWA</th>
<th>HR</th>
<th>PEP</th>
<th>Rectal temp.</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>0.16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEP</td>
<td>-0.14 *</td>
<td>-0.28 *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal temp.</td>
<td>-0.06</td>
<td>-0.03</td>
<td>-0.04</td>
<td></td>
</tr>
<tr>
<td>Foot temp.</td>
<td>-0.07</td>
<td>0.09</td>
<td>0.03</td>
<td>0.14</td>
</tr>
</tbody>
</table>

The correlations reported are for n=10 except for correlations with foot temperature where n=9. * represents p<0.05 (see statistical analysis section for description of how the significance of the mean correlations were calculated).

Table 3—Mean Pearson product moment correlations between slow-wave activity and the remaining variables during the first NREM period of the sleep phase

<table>
<thead>
<tr>
<th></th>
<th>SWA</th>
<th>HR</th>
<th>PEP</th>
<th>Rectal temp.</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>0.23 *</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEP</td>
<td>-0.09</td>
<td>-0.22 *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal temp.</td>
<td>-0.26</td>
<td>-0.30</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>Foot temp.</td>
<td>0.24 *</td>
<td>0.36</td>
<td>-0.17</td>
<td>-0.59</td>
</tr>
</tbody>
</table>

The correlations reported are for n=10 except for correlations with foot temperature where n=9. * represents p<0.05 (see statistical analysis section for description of how the significance of the mean correlations were calculated).

Mean core temperature significantly decreased (by 0.03°C, p=0.02) from NREM to REM sleep in cycle 3 only (Fig. 2). Mean foot temperature significantly increased from NREM to REM sleep only in cycle 1(by 1.34°C, p=0.014; see Fig. 2).

Transition Analysis

All F statistics are reported in Table 4. As illustrated in Figure 3, SWA decreased significantly from NREM to REM sleep in all cycles. SWA increased significantly from REM to NREM in the transition between cycles 1—2, but not in the transition between cycles 2—3. HR did not significantly increase from NREM to REM sleep in cycle 1 but did in cycle 2 (by a mean maximum of 2.89 beats/min) and cycle 3 (by a mean maximum of 4.16 beats/min). From REM to NREM sleep there were no significant changes. There were no significant changes in PEP or rectal temperature. Foot temperature did not significantly alter from NREM to REM sleep. It did significantly increase from REM to NREM sleep in the transition between cycle 1—2 (by a mean maximum of 0.22 deg. C), but not between cycle 2—3.

Correlational Analyses

SWA was not strongly related to any of the cardiac or temperature variables. However, HR and PEP were moderately negatively correlated, indicating that as HR increased, PEP decreased (cardiac sympathetic activity increased) (see Table 2). As all of the variables exhibited major alterations in the first NREM period of the sleep phase, the correlations were also calculated for only the data from the first NREM period (see Table 3). Notable alterations in the correlations were between the temperature and cardiac variables; rectal temperature and HR were moderately...
negatively correlated, as were rectal and foot temperatures. Foot temperature was positively correlated with HR.

**DISCUSSION**

The results replicate previous reports of alterations in SWA and HR across NREM/REM sleep cycles, and extend prior research by describing the variations in PEP, rectal and foot temperature. Mean SWA displayed an ultradian variation in addition to the linear decrease across the night. Previous work has found similar patterns despite the alternative bandwidth (0.33-3 Hz) for SWA used here (e.g., 17.0.75-4.5 Hz.).

The time course and the magnitude of the mean maximum decrease in HR from early NREM to late NREM sleep found here (5.6 beats/min) is similar to previous reports (4.3 beats/min,7). A proportion of this decrease in HR is due to a circadian influence as a smaller decrease is observed when subjects are awake during their normal sleep period (3.1 beats/min,9). During transitions from NREM to REM sleep, mean HR increased (by a maximum of 3.2 beats/min), particularly toward the end of the sleep phase when REM density and length of REM episode are increased.18 As others have also found,16 this increase in HR was evident minutes before the onset of REM sleep. An important contributing factor to the magnitude of the increase in HR is an abrupt deceleration in HR that occurs prior to the onset of REM sleep (see Fig. 1;19-20).

For the first time, this study examined cardiac sympathetic activity (as reflected by the reciprocal of PEP) across NREM-REM cycles. Sympathetic activity increased early in the sleep phase and then progressively decreased, thus accounting for the early increase in HR. The pattern of change in cardiac sympathetic activity observed here is very similar to that in Stage 2 NREM sleep across a nighttime sleep period.7 In contrast, a previous study that sampled PEP hourly during nighttime sleep found sympathetic activity decreased in the first half of the sleep period and then increased in the second half.4 While this earlier study did not control for sleep stage, the maximum increase in PEP was of similar magnitude to that reported here (13.8 and 10.5 m sec, respectively).

The impact of REM sleep (particularly phasic REM sleep) on sympathetic activity may have been underestimated here for two reasons. First, by the averaging of the data into long NREM and short REM periods. Second, by an abrupt increase in diastolic blood pressure (afterload) during phasic REM sleep potentially lengthening PEP. Despite the recording of blood pressure during sleep being somewhat problematic (the inflation of finger cuffs can disturb sleep), reports have indicated that blood pressure increases during phasic REM sleep.21 This abrupt increase in blood pressure would cause PEP to no longer accurately reflect cardiac sympathetic activity. Thus, it is our view that cardiac sympathetic activity is likely to increase with phasic REM sleep, despite PEP not reflecting this. It is important to note however, that the confounding effect of blood pressure on PEP is likely to be limited to the abrupt increases in blood pressure with phasic REM sleep. This is because reports studying blood pressure across entire sleep periods, have found decreases in systolic and diastolic blood pressures.22 Therefore, if any slow trends in blood pressure did systematically alter PEP, this would be in the direction of shortening PEP and not the lengthening as observed here (see Fig 1). Thus the increase in PEP across the night does indeed represent a general down regulation of cardiac sympathetic activity.

The decrease in rectal temperature early in sleep phase was paralleled by an early increase in foot temperature, that then reached a plateau. These findings are consistent with previous reports (e.g.,21), and are likely to be due not only to sleep onset, but also the associated postural and light changes. To our knowl-

---

### Table 4—The F-statistics from the analysis of the NREM/REM sleep transitions

<table>
<thead>
<tr>
<th></th>
<th>SWA</th>
<th>HR</th>
<th>PEP</th>
<th>Rectal temp.</th>
<th>Foot temp.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NREM1/REM1</td>
<td>4.65 *</td>
<td>1.88</td>
<td>1.93</td>
<td>0.42</td>
<td>1.41</td>
</tr>
<tr>
<td>REM1/NREM2</td>
<td>4.28 *</td>
<td>0.99</td>
<td>0.71</td>
<td>0.85</td>
<td>3.78 *</td>
</tr>
<tr>
<td>NREM2/REM2</td>
<td>11.02 *</td>
<td>2.89 *</td>
<td>0.46</td>
<td>1.13</td>
<td>1.28</td>
</tr>
<tr>
<td>REM2/NREM3</td>
<td>1.44</td>
<td>0.82</td>
<td>0.46</td>
<td>1.16</td>
<td>1.68</td>
</tr>
<tr>
<td>NREM3/REM3</td>
<td>14.16 *</td>
<td>3.44 *</td>
<td>2.48</td>
<td>2.19</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Note that the degrees of freedom for all of the reported F-tests are 5 and 45 except for the foot temperature analyses where they are 5 and 40. *indicates p < 0.05. Refer to results section and Figures 3-4 to aid interpretation.

---

![Figure 4](https://example.com/fig4.png)

Figure 4—The average time course of rectal and foot temperature (degrees Celsius) from 3 minutes before to 3 minutes after the first 3 NREM-REM and 2 REM-NREM sleep transitions. These transitions are represented by N-R and R-N respectively. The center line represents the mean for 10 young healthy subjects for rectal temperature and 9 healthy subjects for foot temperature. The upper and lower lines represent ±1 SEM. The asterisks indicate where the change during the transition was significant (p<0.05).
edge, we also examined for the first time in humans, changes in core and peripheral temperatures during transitions between NREM and REM sleep. Rectal temperature only changed from NREM to REM sleep in the third cycle. This decrease is likely to be due to the marked decreased thermoregulatory capacity in REM sleep, that results in core temperature passively decreasing in response to ambient temperature. Importantly, this effect is small when compared to the circadian modulation and sleep onset induced decrease in rectal temperature, and in our data represented only 25.1% of the early decrease. Foot temperature also changed during sleep, but these results are unlikely to represent the direct effects of sleep per se. Instead they are most likely due to these data being positioned at a time when underlying foot temperature was increasing in order to decrease rectal temperature and between subject variability was low.

As HR, rectal and foot temperatures are either strongly influenced by the circadian system (e.g.,4) and/or the onset of sleep, it is not surprising that they did not show a strong relationship with SWA. However, as it has been indicated that cardiac sympathetic activity is not strongly influenced by the circadian system, it is somewhat surprising that cardiac sympathetic activity is not systematically related to NREM sleep intensity. Instead, the main trend in cardiac sympathetic tone is a down regulation across sleep, such that as time asleep continues, the decrease becomes larger. As the main (circadian mediated) increase in cardiac parasympathetic tone is quite early in nighttime sleep,4 our results indicate that cardiac slowing after the first hour of sleep is mainly due to the progressive decrease in cardiac sympathetic tone. Thus, the amount of time spent asleep is an important determinant of cardiac slowing during sleep. Therefore, fragmented nighttime sleep or naps during the day are unlikely to produce the same extent of cardiac slowing as a consolidated period of nighttime sleep. This suggests that a series of naps designed to compensate for extended wakefulness, will not be as physiologically restorative as a single consolidated period of sleep of the same total duration.

While this study was observational in nature, it is interesting to speculate on how the alterations in cardiac activity and temperatures may be linked, particularly during the first NREM sleep period. The increase in foot temperature (heat loss) is most likely driving part of the decrease in rectal temperature. A decrease in peripheral sympathetic tone is likely to have led to increased peripheral vasodilatation thereby producing the increase in foot temperature. In turn, the decrease in peripheral sympathetic tone could well lead to a decrease in blood pressure, thus activating the baroreceptor reflex and so producing a reactionary increase in cardiac sympathetic activity and HR.25 In support of this, there have been reports of decreases in systolic and diastolic blood pressures during sleep (e.g.22), and an increase in cardiac sympathetic activity was evident here early in the sleep period. If this proposed cycle of events is accurate, this suggests that alterations in thermoregulation may account for part of the increase in HR observed shortly after sleep onset. Therefore, in the first hours of nighttime sleep, HR may no longer accurately parallel heat production as it has been reported to during prolonged wakefulness.26

To further investigate the influence of SWA on cardiac sympathetic activity, future work should consider varying SWA by altering prior wakefulness. Such a study may indicate a stronger relationship between SWA and cardiac sympathetic activity.

Further work is required to quantify the degree to which thermoregulatory changes early in sleep drive alterations in cardiac activity.

ACKNOWLEDGMENTS

This work was supported by an Australian Research Council grant to D. Dawson and H.J. Burgess. We thank Sally Ferguson and Saul Gilbert for their comments on the manuscript.

REFERENCES


