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Cardiac Autonomic Activity During Human Sleep: Analysis of Sleep Stages and Sleep Cycles

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Abstract

In this study characteristics of cardiac functioning were investigated in nine subjects during their nocturnal sleep. The pre-ejection period and the high frequency component of heart rate variability were used as indices of cardiac sympathetic and parasympathetic activity of the autonomic nervous system respectively. Heart rate and the autonomic indices were assessed across physiological determined sleep stages and consecutive temporal sleep cycles. Repeated measures ANOVA analyses indicated a significant pattern of heart rate as a function of sleep stages, which was mirrored by parasympathetic activity. Further, a significant decrease of heart rate as a function of sleep cycles was mirrored by an increase of sympathetic activity. Moreover, non-REM/REM differences revealed a dominant role of parasympathetic activity during sleep stages as well as sleep cycles. These findings demonstrate that sympathetic activity is influenced by time asleep, whereas parasympathetic activity is influenced by the depth of sleep.

Keywords: Sleep stages, sleep cycles, heart rate, parasympathetic nervous system activity, sympathetic nervous system activity.

Introduction

Recent constant routine studies have examined potential circadian influences on cardiac autonomic activity (Burgess et al., 1997, Kräuchi et al., 2000). The results from these studies revealed that the respective tonic levels of the two autonomic nervous system components 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, parasympathetic nervous system (PNS) activity appears to be predominantly influenced by the circadian system, such that it

fluctuates in a sinusoidal pattern, while sympathetic nervous system (SNS) activity is mainly influenced by sleep and linearly decreases across nonREM sleep stages 1–4. However, these results are challenged by reports of sleep-induced changes in PNS activity. Specifically, the use of spectral analysis techniques has produced consistent findings that suggest that PNS activity as reflected in the high frequency (HF) spectral band, increases from wake to NREM sleep (often increasing progressively across the four NREM stages) and decreases from NREM to REM sleep (Bonnet & Arand, 1997; Ferini-Strambi & Smirne, 1997; Elsenbruch et al., 1999; Trinder et al., 2001). Measurements of SNS activity, by means of pharmacological blockade, revealed that sympathetic input remains relatively constant throughout all stages of sleep (Zemaityte et al., 1984).

In all, the issue on whether PNS and SNS activity are affected by sleep characteristics or time (i.e., circadian influences) remains unresolved. The present study aimed to contribute to these issues by examining cardiac autonomic activity during successive sleep stages, in order to examine the influence of sleep characteristics and time on heart rate (HR), as well as measures of PNS and SNS activity.

Materials and Methods

Subjects

Nine subjects (4F, 5M) participated in this study (mean ± SD age: 22.3 ± 2.8 years). All participants were undergraduate students at Leiden University, The Netherlands. Prior to the onset of the experiment the participants were screened for a normal sleep-wake rhythm (mean habitual bed-in time 23:16 ± 0:32 h; bed-out time 07:48 ± 0:41 h). The subjects were free of physical illness, nonsmokers (<5 cigarettes/day), and not taking any medication (currently or in the past three weeks), regular heavy caffeine (<350 mg/day), or alcohol (<5 standard drinks/week). The subjects participated in a moderate amount of physical exercise (≥6 h/week) and had no known personal or family history of sleep disorders, or major psychopathology. Subjects reported not to have had any shift work or transmeridian travel in the past 3 months, or any accidents or surgery in that period of time. They were not experiencing any major life stress and had no examinations scheduled for a few days before, during, or after the study. All subjects gave written informed consent before participation and received financial reimbursement for their time.

Procedure

The study was conducted in the sleep laboratory at the Faculty of Social Science, University of Leiden, The Netherlands. The environment in which subjects resided during the experiment was closed off from the external world (located at ground level), temperature conditions (18°C) were kept constant, and the level of illumination never exceeded 100 lux. The private bedroom held an infrared source and two infrared sensitive camera's; one to monitor the subject's face and one for a wide angled overview of the bedroom. Also, an intercom was present right behind the top of the

bed. After the screening and consent procedures, subjects received a wrist activity monitor (Gaewhiler), were instructed to refrain from physical exercise and naps, as well as caffeine and alcohol consumption at least five hours prior to sleep onset, and left the sleep laboratory. That evening, subject were expected to be back at 21:30 h for the registration night. Electrodes for polysomnographic recordings as well as electrocardiogram (ECG) and impedance-cardiogram (ICG) recordings were then appended to the subject. All subjects were put to bed and lights were turned off between 23:00 and 00:00 h, depending upon their habitual bed-in/bed-out times. One experimenter was present at the sleep laboratory facility during the entire recording period in a separate control room. In this control room, the electro-encephalogram (EEG) recordings were visible online on a computer screen. A TV-monitor connected to the infrared sensitive cameras inside the bedroom gave information on possible wake-state and movements of the subject. Subsequently, a time-lapse video recorder taped the entire night, and was synchronized with the EEG recording computer. The intercom gave the subject the opportunity to alert the experimenter for possible toilet requirements. Between 7:30 and 08:00 h, subjects were awakened and all electrodes were removed.

Assessment of cardiac variables

The cardiac measurements were made with the Vrije Universiteit Ambulatory Monitoring System (VU-AMS) version 4.3. This device uses six Ag/AgCl electrodes to record HR and thoraric impedance (dZ). Details on electrode placement and R-spike detection of this device can be found in de Geus et al. (1995). Cross-instrumental comparison of the VU-AMS with a standard laboratory measurement set-up showed excellent between-subjects and within-subjects correlation of respiratory rate, respiratory sinus arhythmia, and spectral heart period powers (De Geus et al., 1995). The offline monitoring device was synchronized with the clock of the EEG recording computer.

The power spectral analysis of heart rate variability (HRV) was carried out with the fast Fourier algorithm. By means of spectral analysis software (CARSPAN) the HF (0.15 Hz–0.50 Hz) and total frequency (TF, 0 Hz–0.50 Hz) component of HRV was derived by a spectral profile analysis over inter beat intervals in 4 minute epochs. All artefacts marked in the log file were later removed. The HF band was then expressed as a proportion of the total frequency (HF/TF ratio).

SNS activity was measured as the isovolumetric contraction time of the ventricle, defined as pre-ejection period (PEP). PEP is obtained by means of alterations in thoracic impedance, and is inversely related to myocardiac contractility. To determine PEP, 30 s ensemble average complexes of the DZ/dt signal (ICG) were visually scored. All artefacts such as movements or other disturbances were marked and removed from further analysis. The cardiac variables were then synchronized and coupled to the EEG data.

Polysomnographic assessment

Ag/AgCl 6 mm electrodes were used for the C3, C4, A1, and A2 scalp locations, Meditrace™ spot electrodes were used for the recordings of the electro-oculogram

(EOG) and the submental electro-myogram (EMG). Polysomnografic recordings were carried out with two central (i.e., C3 and C4) EEG channels and were amplified by a PSA-24 amplifier, jointly with two EOG and EMG channels. Thirty-second epochs were extracted from the data. The sleep stages 1–4 and REM were scored visually by two trained scorers according to the standards of Rechtschaffen and Kales (1968). The delineation of the successive NREM/REM cycles was carried out according to the standards of Feinberg and Floyd (1979). NREM/REM cycles can be considered to constitute a 'physiological' time scale, and as such represent the factor time.

All epochs containing sleep disturbance (wake state, movement time) were marked and removed at a later stage of data processing.

Analysis

The design used in this study was a repeated-measures ANOVA with Stage (five levels) and Cycle (four levels) as within-subjects factors. Furthermore, the within subject factor NREM-REM (two levels) was used in the cycle analysis to examine NREM sleep versus REM sleep dependency as a function of time asleep. The violation of the sphericity assumption using repeated-measures ANOVA was corrected by the Huynh-Feldt correction factor epsilon (ε) (Jennings, 1987; Keselman, 1998). Also t-tests were carried out to determine differences in mean NREM-REM values.

Results

Sleep stages

HR data were analyzed as a function of sleep stages. Figure 1a shows that mean values of HR moderately decline over the course of the stages 1–4, followed by a sharp increase during REM periods. Repeated measures ANOVA yielded a significant result for the factor Stage: $F[4,32] = 4.318$, $p = 0.016$, $\varepsilon = 0.706$. Moreover, a paired sample t-test showed a significant difference between NREM vs. REM values of HR ($t(8) = 2.416$, $p = 0.042$), with lower values during NREM sleep as compared with REM sleep.

Analysis of the PEP data showed an unclear pattern over the course of sleep stages. As seen in Figure 2a, mean values fluctuate around a PEP value of 121 ms, with a range of less than 2 ms. As expected, no significant effect was found for the factor Stage: $F[4,32] = 0.991$, $p = 0.414$, $\varepsilon = 0.752$. Moreover, a paired sample t-test failed to show a significant difference between NREM versus REM values of PEP: $t(8) = 0.041$, $p = 0.968$.

As seen in Figure 3a, mean values of the HF/TF ratio show a robust pattern that roughly mirrors the result of HR. A steady linear increase during stages 1–4 is followed by a sharp decrease during REM periods. This gave a significant effect on the factor Stage: $F[4,32] = 27.799$, $p < 0.001$, $\varepsilon = 0.846$. Moreover, a paired sample t-test showed a significant difference in NREM versus REM values of HF/TF ratio: $t(8) = -5.321$, $p = 0.001$, with higher values during NREM sleep as compared with REM sleep.
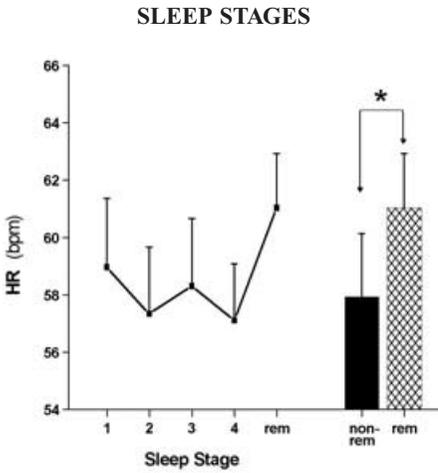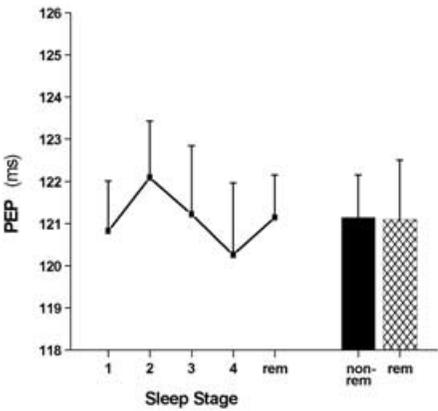
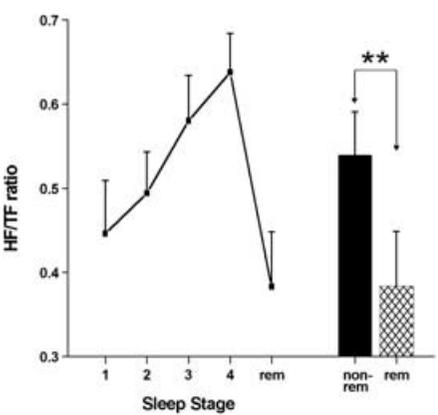**SLEEP STAGES**　　　　**SLEEP CYCLES**

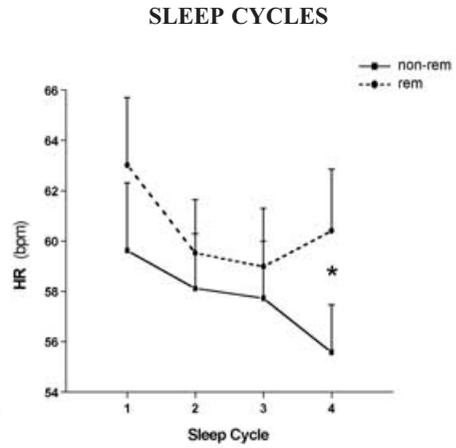*Fig. 1a*　　　　　　　　　*Fig. 1b*
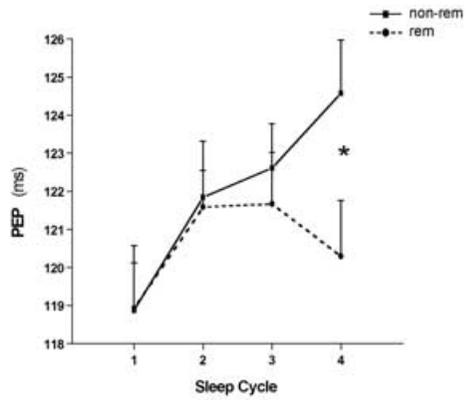

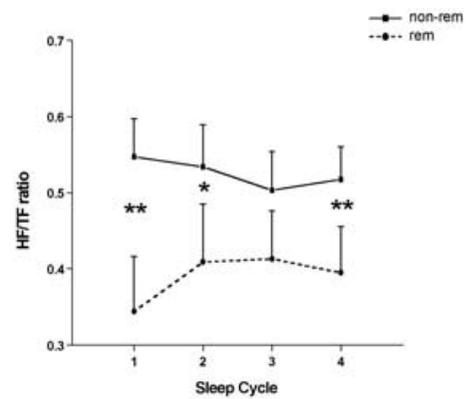
Fig. 2a　　　　　　　　　*Fig. 2b*

Fig. 3a　　　　　　　　　*Fig. 3b*

Figures 1a–3b. HR, PEP, and HF/TF ratio over sleep stages and NREM-REM sleep comparison, as well as over sleep cycles for NREM sleep and REM sleep ($N = 9$). Bars represent standard error of mean. Asterics indicate level of significance: $*$ = $p < 0.05$, $**$ = $p < 0.01$.

Sleep cycles

In addition, the data were analyzed as a function of the successive sleep cycles. As seen in Figure 1b, mean values of HR during NREM sleep decline over the course of time, that is, over the successive sleep cycles (F[3,24] = 3.844, p = 0.038, ε = 0.497). This pattern was similar for REM-sleep (F[3,24] = 6.491, p = 0.009, ε = 0.654), but only during the first three cycles. During cycle four, HR shows a moderate rise during REM-sleep. Overall, the decrease of HR gave a significant effect on the factor Cycle: F[3,24] = 4.704, p = 0.040, ε = 0.488. Paired sample t-test showed a significant difference in NREM vs. REM values of HR only during the fourth cycle: t(8) = −3.387, p = 0.010.

As seen in Figure 2b, PEP shows a significant increase over the course of sleep cycles during NREM sleep: (F[3,24] = 7.247, p = 0.004, ε = 0.774). During REM sleep, a nonsignificant pattern is shown: (F[3,24] = 1.847, p = 0.179, ε = 0.808). Whereas PEP values during REM sleep parallel those in NREM sleep during the first three cycles, they clearly differ for the fourth cycle (t(8) = 3.228, p = 0.012). As a result, a significant effect of NREM/REM × Cycle interaction was found (F[3,24] = 5.317, p = 0.012, ε = 0.771).

The HF/TF ratio remained roughly unchanged over the course of time, and failed to show an overall significant effect on the factor Cycle: F[3,24] = 0.273, p = 0.844, ε = 1.000. Also, analysis of NREM and REM patterns separately yielded no significant effects, as can be seen in Figure 3b. Furthermore, no significant effect of NREM/REM × Cycle interaction was found: F[3,24] = 2.022, p = 0.182, ε = 1.000. The NREM and REM values showed significant differences for the first cycle (t(8) = 5.307, p = 0.001), the second cycle (t(8) = 2.781, p = 0.024), and the fourth cycle (t(8) = 3.823, p = 0.005), but not for the third cycle (t(8) = 1.696, p = 0.128).

Table 1.   Sleep parameters over the entire sleep period.

Sleep Stages	Sleep Cycles				
	Total	1	2	3	4
Stage 1	74.9 (15.7)	12.2 (3.4)	13.9 (3.2)	27.8 (6.0)	21.1 (8.5)
Stage 2	139.4 (13.2)	26.6 (6.5)	43.0 (3.7)	44.9 (5.5)	24.9 (9.6)
Stage 3	40.2 (3.1)	17.6 (3.0)	7.8 (2.3)	8.8 (3.5)	5.9 (2.8)
Stage 4	46.8 (8.5)	25.9 (4.3)	16.4 (4.7)	4.4 (2.9)	0.00 (0.00)
REM	53.9 (6.2)	7.9 (7.1)	13.0 (2.2)	14.6 (5.5)	18.4 (3.7)
Cycle duration		90.3 (8.2)	94.1 (6.1)	100.5 (6.3)	70.3 (20.5)
Midpoint cycles (in hours)		01:48 h	03:31 h	05:11 h	6:54 h

Mean duration (standard error of mean) of sleep stages over sleep cycles in minutes (N = 9).

Discussion

In this study, cardiac activity, as measured by HR and indices of PNS and SNS activity, was investigated in relation to the neurophysiological characteristics of sleep. Two primary results were obtained. PNS rather than SNS activity appeared to covary with the depth of sleep, whereas SNS and not PNS activity changed systematically as a function of time asleep. Both autonomic influences had their impact upon HR.

With respect to the sleep-related effects, the data are broadly consistent with the major trends in the literature as to the stage dependent variations of cardiac activity. In particular, HR decreased from stage 1 to stage 4 against a background of increasing PNS activity (HF), while REM sleep was characterized by increased HR and decreased PNS activity (see also Zamaityte et al., 1984; Somers et al., 1993). SNS activity as reflected in the PEP measure failed to show significant variations across sleep stages (see also Trinder et al., 2001).

The results from the current sleep cycle analysis partly replicate previous findings for the time course of changes in HR, SNS and PNS activity. Thus, earlier studies reported a linearly declining trend in HR over successive NREM and REM periods (Cajochen et al., 1994; Versace et al., 2003), an increase in SNS activity during the sleep period (Burgess et al., 1997, 1999, 2001; Trinder et al., 2001), and no variation in PNS activity as a function of time (Trinder et al., 2001), results that are similar to the findings presented in this study. In respect to NREM-REM effects as a function of time, the present results show divergence of NREM and REM values of HR and SNS activity only in the fourth cycle, when REM sleep is most predominant. Recent investigations showed no NREM-REM differences for HR (Burgess et al., 2001; Versace et al., 2003) and SNS activity (Burgess et al., 2001; Trinder et al., 2001) across the sleep period. PNS activity consistently showed a marked difference between NREM and REM over time during sleep (Trinder et al., 2001). However, divergence in HR across NREM and REM episodes (Trinder et al., 2001) and an absence of NREM-REM effects for HF during the second, third, and fourth sleep cycle (Versace et al., 2003) were also reported.

A previous study on PNS activity during a 24 h sleep deprivation (i.e., constant routine) condition reported a clear increase in PNS activity during the period of the night, indicating a circadian periodicity of PNS activity (Burgess et al., 1997). SNS activity recorded during night-sleep also suggested a time dependency, as it showed a marked increase across the consecutive NREM episodes. However, this may not be interpretable as a circadian effect, as it has been shown that the PEP measure does not change across the night under the unmasked (sleep deprived) conditions of a constant routine protocol (Burgess et al., 1997). Therefore, the SNS variation across the sleep period is more interpretable as an effect of time asleep. It can be postulated that SNS activity is particularly responsive to exogenous stimuli and is not, or only moderately, modulated by a circadian factor. Even when subjects are relatively isolated from exogenous influences, as during a constant routine procedure, SNS activity is maintained at a constant level. Only during sleep, when exogenous influences are minimized, SNS activity gradually decreases to low levels.

The absence of a time dependent effect in the HF measure of the present study forms an inconsistency with earlier findings of strict circadian regulation of PNS activity (Burgess et al., 1997). It could be suggested that, supported by the sleep stage results and the clear NREM-REM effects across the sleep cycles, the circadian modulation of HF is masked by the sensitivity of PNS activity to sleep stage transitions. Future research could focus on the separation of sleep and circadian influences on the autonomic control of cardiac activity by means of forced desynchrony or related protocols.

Acknowledgements

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