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Heart Rate Dynamics During Human Sleep

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CAJOCHEN, C., J. PISCHKE, D. AESCHBACH AND A. A. BORBÉLY. *Heart rate dynamics during human sleep.* PHYSIOL BEHAV 55(4) 769–774, 1994.—To investigate the dynamics of heart rate in the course of sleep and to relate cardiac activity to sleep intensity, the electrocardiogram was recorded concomitantly with the polysomnogram in healthy young males. Heart rate was assessed across consecutive non-REM sleep (NREMS)-REM sleep (REMS) cycles as well as within individual episodes of NREMS and REMS. Within a sleep cycle, heart rate was lower in the NREMS episode than in the subsequent REMS episode. A global declining trend was present over successive NREMS episodes and over successive REMS episodes. A rapid increase of heart rate at the NREMS–REMS transitions was followed by a slow decline that started within the REMS episodes. Heart rate variability was higher in REMS than in NREMS and showed an increasing trend over successive REMS episodes but not over successive NREMS episodes. EEG slow-wave activity (spectral power density in the 0.75–4.5 Hz band), an intensity measure of NREMS, declined across NREMS episodes and was not correlated with heart rate. The global trends and ultradian variations of heart rate may represent sleep state-dependent modulations and circadian variations of the autonomic nervous system, which are not fully reflected in the sleep EEG.

Sleep Heart rate Electrocardiogram Slow-wave activity Spectral analysis

IT has long been known that heart rate is affected by sleep and that it shows a declining trend in the sleep episode [see (18)]. In their pioneering description of REM sleep (REMS) Aserinsky and Kleitman (2) noted a 10% increase in heart rate in REMS as compared to the preceding and following non-REM sleep (NREMS). Not only heart rate itself but also the beat-to-beat variability was found to be higher in REMS than in NREMS (16). Although these observations were confirmed and extended by Snyder et al. (24), a detailed, quantitative analysis of the time course of these changes has not been performed.

Also, systematic changes within NREMS have been reported. Thus, a slowing of cardiac activity was reported to accompany the transition from the superficial stage 1 to the deepest stage 4 (17,29) or from stage 2 to stages 3 and 4 (24), and even a sleep stage classification based on heart rate data was attempted (28). In a recent study (25), lower levels of blood pressure and sympathetic nerve activity were observed in stage 3 and 4 than in stage 2, whereas heart rate was not significantly different. One of the aims of the present study was to further examine and clarify the relationship between heart rate and NREMS intensity. This analysis was based on EEG slow-wave activity (SWA; spectral power density in the 0.75–4.5 Hz band), a parameter that has proved to be a reliable indicator of NREMS intensity (6,7,11,12,23). In addition, SWA is used as measure of the homeostatic sleep regulatory process as its level in the first NREMS episode is determined by the duration of prior waking (7,10). In the course of sleep, SWA exhibits a global declining trend as well as ultradian variations. Within each NREMS episode, it shows a progressive buildup to a peak or plateau level, and a precipitous decline prior to REMS. The initial, intraepisodic buildup rate declines over successive NREMS episodes (1,11,20).

The main objectives of the present study were to perform a quantitative analysis of heart rate during sleep, focusing both on global trends over the entire sleep episode and on the changes related to the NREMS–REMS cycle. Specific questions were:

1. whether the modulation by the NREMS–REMS cycle is equal throughout the sleep episode;
2. whether trends are present within episodes of NREMS and REMS or if changes occur exclusively at state transitions; and
3. whether cardiac activity is associated with the changes in sleep intensity as indexed by SWA.

METHODS

Subjects

Sixteen recordings were obtained from eight healthy young male subjects (mean age 24.1; range: 23–26 years) who were asked to refrain from alcohol, excessive caffeine consumption, and daytime naps during the experiments. Wrist-worn activity monitors were used to check compliance to the latter instruction. Subjects with sleep complaints, a significant medical history, or drug use were excluded from the study. Each subject was recorded for two nights, one week apart, each preceded by an adaptation night. Due to technical problems the data of one night of one subject could not be used. The recordings were obtained

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TABLE 1

SLEEP PARAMETERS IN THE ENTIRE SLEEP EPISODE AND THE FIRST FOUR NREMS-REMS CYCLES

Sleep Parameters (min)	Sleep Episode	NREM-REM Sleep Cycle			
		1	2	3	4
Total sleep	448.1				
time	2.7				
Sleep latency	17.8				
	2.5				
REMS latency	81.5				
	5.6				
Waking (W)	5.2	1.4	0.7	0.5	1.4
	1.5	0.8	0.3	0.2	0.6
Stage 1	31.6	3.6	6.7	6.9	7.4
	3.3	1.0	1.2	1.1	1.0
Stage 2	220.6	34.0	53.9	55.4	47.3
	7.3	5.8	4.8	7.0	2.0
Stage 3	50.1	15.4	14.2	13.7	3.3
	3.5	1.1	1.4	2.2	1.2
Stage 4	48.1	27.9	9.1	9.2	1.6
	8.6	5.2	1.6	2.4	1.5
Slow wave	98.2	43.3	23.3	22.9	4.9
sleep (SWS)	10.7	5.2	2.6	3.7	2.6
REM sleep	97.8	10.4	27.2	23.2	26.7
	5.8	2.4	2.0	3.6	5.2
Movement time (MT)	8.1	1.5	2.0	2.2	1.5
	1.2	0.3	0.4	0.5	0.3
MT + W + 1	44.9	6.6	9.3	9.5	10.3
	3.9	1.9	1.5	1.5	1.2
Cycle duration		94.3	113.8	111.0	89.2
		7.1	4.8	9.1	7.3

Mean values (n = 8; 15 nights) with SEM are expressed in minutes. Sleep latency is defined as the first occurrence of stage 2 and REM sleep latency is measured from sleep onset. REMS episode 4 was <5 min in 2 nights.

between 2300 h and 0700 h in the sound-attenuated and completely darkened bedrooms of the sleep laboratory.

Polygraphic Recordings

The surface ECG (modified bipolar V5 lead), EEG (C3/A2 or C4/A1), submental EMG, and EOG were recorded. Self-adhesive silver-chloride electrodes (Sensor Medics, Skin electrode kit) were used for placements on the skin and silver disk electrodes (Grass Instruments, Type E5 SH) fixed with collodium for placements on the scalp. All electrodes were filled with electrode cream (Synapse®). The signals were amplified (Grass 7P122E polygraph amplifier, time constant of 0.8 s, for ECG; Grass 7P511K, time constant of 0.9 s, for other signals). The combined action of the amplifier's 50 Hz notch filter and an analog low-pass filter served to attenuate high frequency components (−3 dB at 27 Hz). The signals were digitized at 128 Hz with 12-bit resolution, digitally filtered (4th order Butterworth filter 24 dB/oct; −3 dB points of low-pass or band-pass filters: EEG, 25 Hz; EOG, 55 Hz; EMG, 20–60 Hz; Compar AG TMS 32025 signal processor card) and stored on the disk of a Personal Computer (PC; Hewlett Packard, QS 80386s/16 MHz). An on-line Fast-Fourier Transform routine (procedure RVFFT from Mathpak87™ by Precision Plus Software, Oakville, Ontario, Canada) was used for the analysis of the EEG. EEG spectra were computed for 4 s epochs and 0.25 Hz bands in the range of 0.25–25 Hz by applying a rectangular window. After visual inspection and elimination of 4 s epochs contaminated by movement artefacts, values were averaged for 20 s epochs. SWA was defined as the power density in the 0.75–4.5 Hz band. The EEG records were visually scored for 20 s epochs according to the criteria of Rechtschaffen and Kales (22). NREMS–REMS cycles were defined according to the criteria of Feinberg and Floyd (13) with the following exception: for the last cycle analyzed (cycle 4) no minimum of REMS duration following upon NREMS was required. For cycles 2–4 the first 20 s epoch following upon the last REMS epoch was defined as the onset of the cycle. The last REMS episode was <5 min in 2 nights of one subject.

Cardiac beat-to-beat intervals, determined as the time between successive R-waves, were detected offline by a level-crossing algorithm (set at 60% of R-wave amplitude). Mean and median cardiac rate per 20 s epoch were calculated throughout the recording. An artefact detection routine designated epochs in which the variability of R-R intervals exceeded a preset value (35% of the standard deviation). Subsequently, the epochs were visually inspected and either corrected or eliminated.

Statistics

For statistical analyses (ANOVA; two-tailed t-test) the SAS statistical package (SAS software, SAS Institute Inc, Cary, NC) was used.

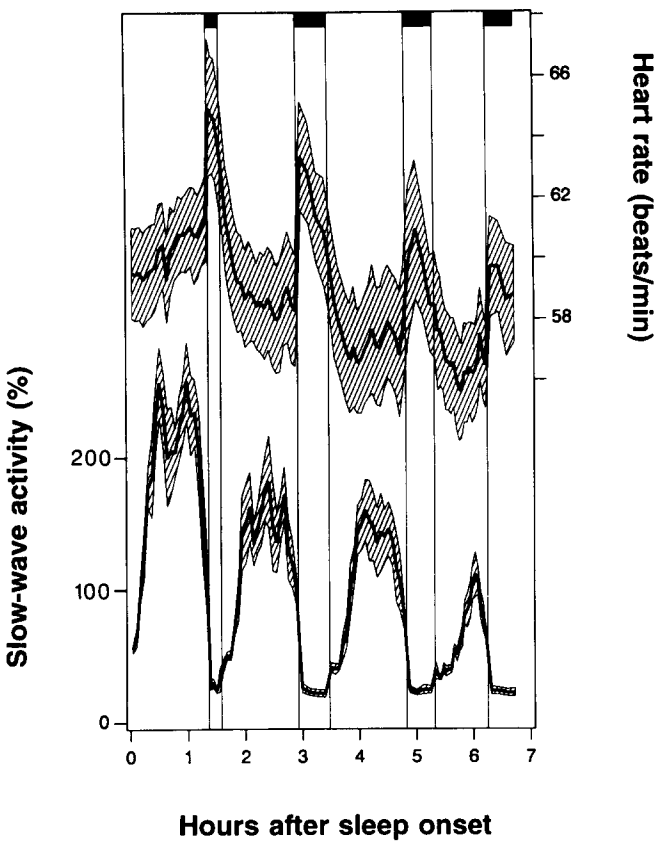

FIG. 1. Dynamics of heart rate and slow-wave activity (SWA). Mean values (n = 8; 15 nights); top bars delimit REMS episodes. SWA is expressed as the percentage of the mean TST value (100%). The curves are plotted relative to the mean onset and termination of each cycle. Hatched areas indicate ±1 SEM.

RESULTS

Sleep Stages

Table 1 summarizes the sleep parameters for each NREMS–REMS cycle and for the entire sleep episode. Because no significant differences were present between the two nights recorded for each subject (paired t-test), the average individual values were used for the analysis.

To assess the changes across cycles, the data were subjected to a one-way ANOVA for repeated measures on the factor cycle. For this analysis SWS, REMS, movement time, waking, and stage 1 (MT+W+1) were expressed as the percentage of total sleep time per cycle. The effect of cycle was significant for both SWS, $F(3, 21) = 29.8, p < 0.001$, and REMS, $F(2, 14) = 15.5$, $p < 0.002$, whereas for MT+W+1 only a tendency was observed, $F(3, 21) = 3.4, p = 0.064$.

SWS decreased from cycle 1 to 4, whereas REMS was shortest in the first cycle (cycle 1 vs. cycle 4: SWS $p < 0.001$; cycle 1 vs. cycle 3: REMS $p < 0.005$).

Time Course of Heart Rate and Slow-Wave Activity (SWA)

The mean values (SEM; n = 8) of heart rate (beats per min) in the three major vigilance states were the following: waking before sleep onset (i.e., lights off to first occurrence of stage 1): 64.9 (2.0); REMS 60.8 (1.8); NREMS 58.5 (1.8). All values differed significantly from each other ($p < 0.05$; paired t-test).

To be able to analyze the time course of the changes on the basis of mean values, each NREMS episode was subdivided into 20 equal parts (percentiles) and each REMS episode into four equal parts (8). For all subdivisions in the first four cycles the mean heart rate and mean SWA within sleep were calculated and averaged over subjects. The average time course of heart rate and SWA is illustrated in Fig. 1.

Heart rate showed a global declining trend during sleep that was present across NREMS episodes as well as across REMS episodes (one-way ANOVA for repeated measures on the factor episode; NREMS, $F(3, 21) = 3.6, p < 0.03$; REMS $F(3, 21) = 23.7, p < 0.001$. Post hoc comparisons on mean episode values revealed a significant trend over the first three REMS episodes but not over successive NREMS episodes (cycle 1 vs. cycle 2, NREMS: $p = 0.38$, REMS: $p < 0.05$; cycle 2 vs. cycle 3, NREMS: $p = 0.09$, REMS: $p < 0.05$; cycle 3 vs. cycle 4, NREMS: $p = 0.06$, REMS: $p = 0.33$, paired t-test).

Within each cycle, the value was lower in the NREMS episode than in the subsequent REMS episode (cycle 1: $p < 0.05$; cycle 2: $p < 0.003$; cycle 3: $p < 0.006$; cycle 4: $p < 0.02$; paired t-test on the mean episode values). In addition, a significant variation was present within REMS episodes 2 and 3 [factor subdivision: episode 2: $F(3, 21) = 13.2, p < 0.001$; episode 3: $F(3, 21) = 3.6, p < 0.05$; one-way ANOVA for repeated measures]. By subdividing NREMS episodes into 10 equal parts a significant variation was revealed within NREMS episode 2 and 4 [factor subdivision: episode 2: $F(9,63) = 5.3, p < 0.01$; episode 4: $F(9, 63) = 3.0, p < 0.05$].

As in previous studies (13), SWA was standardized by expressing it as a percentage of mean SWA in total sleep for each night. SWA showed a declining trend across the four NREMS episodes [factor episode: $F(3, 21) = 36.3, p < 0.001$; one-way ANOVA for repeated measures].

The correlation coefficients of SWA and heart rate (individual values computed over all percentiles) did not differ significantly from zero (mean correlation coefficients of individual values; NREMS: $r = 0.29, p > 0.05$; REMS: $r = 0.29, p > 0.05$; n = 8, t-test on Fisher z-transformed correlation coefficients).

Changes of Heart Rate at Episode Transitions

To investigate the changes of heart rate at the transitions between NREMS and REMS in more detail, 1 min values were computed for the 5 min interval before and after transitions (Fig. 2). The data were expressed as the deviation from the transition value which was defined as the mean between the 1 min pretransition and 1 min posttransition values. After computing the mean over subjects, the mean absolute transition value was added for plotting the curves in Fig. 2. Twenty second epochs with waking or movement time were excluded from the calculations.

Figure 2 shows that the heart rate increased rapidly over the NREMS–REMS transition periods and decreased more gradually at the REMS–NREMS transition periods. The ANOVA for repeated measures with factor time (1 min values) was significant for each NREMS–REMS transition [cycle 1: $F(9, 63) = 8.1, p < 0.003$; cycle 2: $F(9, 63) = 20.8, p < 0.001$; cycle 3: $F(9, 63) = 3.9, p < 0.05$; cycle 4: $F(9, 63) = 9.7, p < 0.002$]. Only the first REMS–NREMS transition reached a significant level, $F(9, 63) = 3.3, p < 0.05$, while a trend was present for cycle 2, $F(9, 63) = 2.1, p = 0.09$.

For each transition with a significant factor time it was tested whether any of the five 1 min pretransition values and/or the five 1 min posttransition values differed from the transition value. Significantly lower pretransition values were observed for NREMS–REMS transitions 1, 2, and 4, and higher posttransition

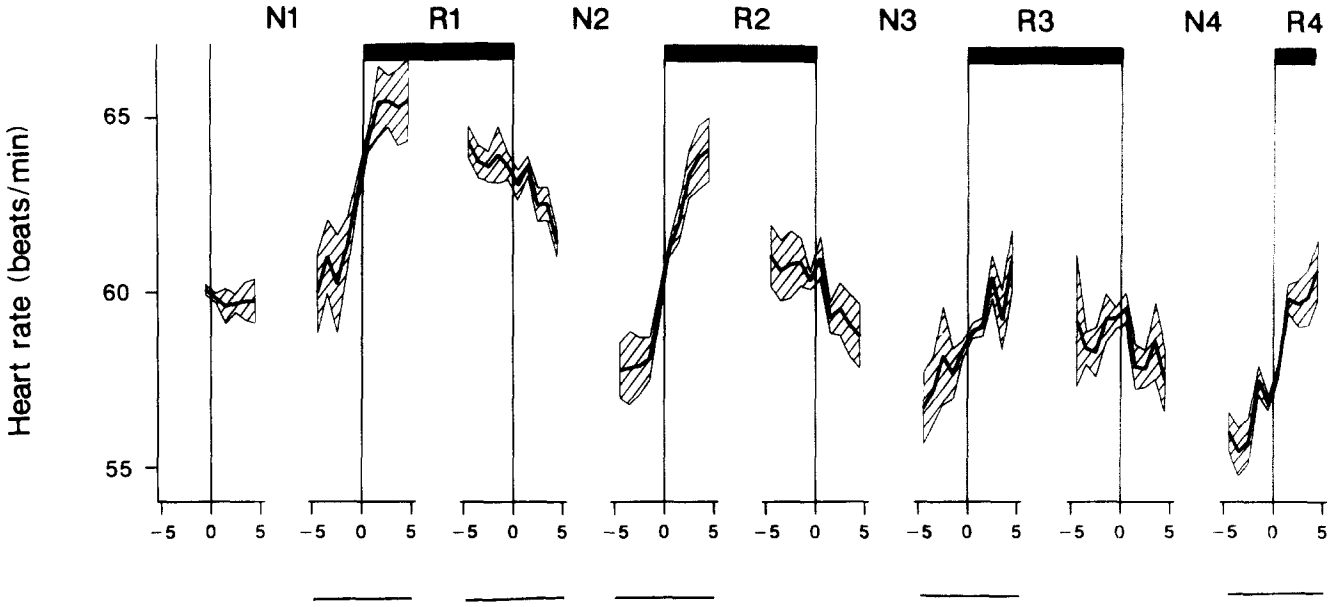

FIG. 2. Heart rate in the intervals 5 min before and 5 min after the episode transition between NREMS (N) or REMS (R) (n = 8; 15 nights). The 1 min value before the onset of the first N-episode is plotted. For calculating the standard errors (hatched area indicates ±1 SEM) the values were expressed as differences from the transition value (vertical reference line at 0 min). Black bars on top indicate REMS episodes. Lines below abscissa indicate significant one way ANOVA for repeated measures ($p < 0.05$, factor time).

values for transitions 2, 3, and 4 ($p < 0.05$; paired t-test). As to the REMS–NREMS transitions, only the fifth 1 min interval after the first transition differed significantly from the transition value.

Heart Rate Variability

The coefficient of variation in heart rate was determined from the R-R intervals for each episode subdivision. The duration of the subdivisions ranged from 2.9 to 4.1 min for NREMS episodes and from 3.3 to 8.3 min for REMS episodes. After computing the mean value per episode, the average episode values over nights and subjects were calculated.

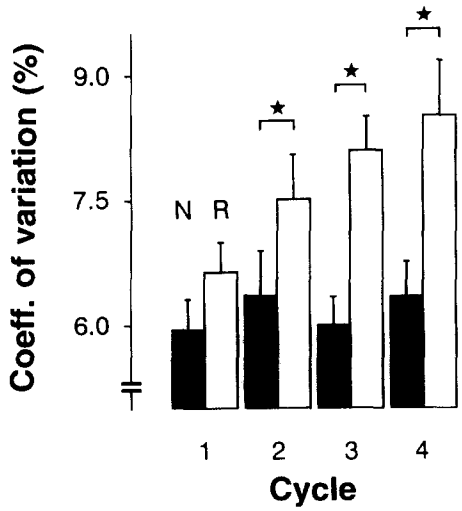

FIG. 3. Coefficient of variation of heart rate in episodes of NREMS (N) and REMS (R) (n = 8; 15 nights; bars represent 1 SEM). Asterisks indicate significant differences between successive episodes of NREMS and REMS (paired t-test; *$p < 0.03$).

Figure 3 shows that the coefficient of variation in heart rate increased progressively over REMS episodes [factor episode: $F(3, 21) = 5.0$, $p < 0.05$; one-way ANOVA for repeated measures], whereas the values for NREMS episodes showed little change [factor episode: $F(3, 21) = 1.4$, $p > 0.05$; one-way ANOVA]. Post hoc comparisons (paired t-test) between episodes revealed significantly higher values for REMS episode 3 ($p < 0.002$) and 4 ($p < 0.05$) in comparison to episode 1. Comparisons within cycles showed significantly higher values for REMS than for NREMS in cycle 2 ($p < 0.03$), cycle 3 ($p < 0.001$), and 4 ($p < 0.005$).

To test whether the length of subdivisions was a critical factor for this result, the calculations were also performed for subdivisions of NREMS episodes into 10 parts (range of durations: 5.9–8.2 min). Similar results were obtained, indicating that the length of subdivisions was not critical.

DISCUSSION

The results demonstrate that heart rate exhibits a global trend as well as ultradian variations within the sleep episode. Although in each cycle the heart rate was consistently lower in NREMS than in REMS, the progressive slowing was evident for both successive NREMS episodes and successive REMS episodes. Thus, the general trend over the entire sleep episode was modulated by the NREMS–REMS cycle.

The present analysis focused in some detail on the changes in heart rate at transitions between NREMS and REMS. A striking feature was the asymmetry in the time course: The rapid cardiac acceleration at the onset of REMS episodes contrasted with the slow deceleration at the end (Fig. 2). Interestingly, heart rate started to increase several minutes before REMS and continued to rise into the REMS episode. This observation supports the

notion that the REMS initiating events occur before the polysomnographic signs of this sleep state. This is in accordance with neurophysiological data in the cat, whose cholinergic brain stem neurons with a high firing rate during REMS increase their discharge rate already 1 min before the NREMS–REMS transition (26). The predominant role of REMS onset for the ultradian modulation of heart rate is further underscored by the observation that in two REMS episodes the highest value was attained in the early part of the episode and that a decline began already during REMS (Fig. 2). Cardiac activity in sleep reflects the state of the autonomic nervous system, and in particular, the balance of the sympathetic-parasympathetic tone (14). Whereas in NREMS the predominance of vagal activity results in a low cardiac output and a reduced total peripheral resistance (21), the marked increase in sympathetic nerve activity during REM sleep reverses these effects (15,25). Although the time course of the changes in the autonomic nervous system have not yet been subjected to a detailed analysis, the present results indicate that the sympathetic activation occurs more rapidly than its deactivation and the rise in parasympathetic activity.

It is reasonable to assume that deep and quiet sleep is associated with a lower heart rate than restless and superficial sleep. As has been stated in the introduction, there is polysomnographic evidence to support this assumption. Moreover, the short-term changes do not appear to contradict this notion, because within each NREMS episode, the buildup of SWA was accompanied by a decline in heart rate (Fig. 1). However, viewed over the entire sleep episode, heart rate was not correlated with NREMS intensity. The overall decline of the NREMS intensity as indexed by the peak values of SWA and the rising tendency of arousal (waking+movement time+stage 1; Table 1) during the night were associated with a progressive slowing of cardiac activity, and not with an acceleration. The factors contributing to the gradual bradycardia could be the recumbent posture, the progression of the sleep process itself, and the circadian pacemaker. The contribution of these factors can be estimated from a study in which a regular nighttime sleep episode was followed by a constant routine protocol in which the subjects remained awake for 40 h in a semirecumbent posture (19). Whereas during sleep the heart rate declined by approximately 4 beats per min (bpm), the decline during the corresponding period of the constant routine amounted to approximately 2 bpm. Although these results suggest that sleep and the circadian pacemaker contribute equally to the nighttime bradycardia, a confirmation by a more detailed analysis is required. The circadian system may have had repercussions also on heart rate variability.

In contrast to the progressive bradycardia that was present in both sleep states, the increasing trend in heart rate variability was limited to REMS (Fig. 3) (24). Because REMS is known to be controlled to a large extent by the circadian pacemaker and exhibits its maximum propensity close to the minimum of core body temperature (9), the rise in heart rate variability over REMS episodes could represent a REMS-related circadian modulation. Moreover, heart rate variations during REMS coincide with phasic events (3,27), which are known to be more frequent in later REMS episodes (4,5). However, not only circadian factors may be involved, because the density of rapid eye movements is inversely related to sleep propensity [see (10) for references]. Recordings of sleep at different circadian phases are needed to further examine this issue.

In conclusion, the analysis of heart rate revealed rapid state-dependent changes and gradual trends that do not simply mirror the variations of EEG parameters. Thus, heart rate represents an informative and easily recorded measure of the autonomic nervous system whose usefulness for delineating sleep processes has not yet been fully exploited.

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