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Clinical Neurophysiology 112 (2001) 992–996

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# Inverse coupling between ultradian oscillations in delta wave activity and heart rate variability during sleep

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Accepted 14 February 2001

**Abstract**

Objective: We investigate the relationship between changes in heart rate variability and electroencephalographic (EEG) activity during sleep.

**Method**: Nine male subjects with regular non-rapid-eye movement-rapid-eye movement (NREM-REM) sleep cycles were included in the study. They underwent EEG and cardiac recordings during one experimental night. Heart rate variability was determined over 5-min periods by the ratio of low frequency to low frequency plus high frequency power [LF/(LF + HF)] calculated using spectral analysis of R-R intervals. EEG spectra were analyzed using a fast Fourier transform algorithm.

**Results**: We found an ultradian 80–120 min rhythm in the LF/(LF + HF) ratio, with high levels during rapid eye movement (REM) sleep and low levels during slow wave sleep (SWS). During sleep stage 2 there was a progressive decrease in the transition from REM sleep to SWS, and an abrupt increase from SWS to REM sleep. These oscillations were significantly coupled in a 'mirror-image' to the overnight oscillations in delta wave activity, which reflect sleep deepening and lightening. Cardiac changes preceded EEG changes by about 5 min.

**Conclusions**: These findings demonstrate the existence of an inverse coupling between oscillations in delta wave activity and heart rate variability. They indicate a non-uniformity in sleep stage 2 that underlies ultradian sleep regulation. 

*Keywords*: Sleep; Electroencephalographic activity; Heart rate variability; Sympathovagal balance; Ultradian rhythm

## 1. Introduction

Some well-defined ultradian rhythms with periods averaging 80–120 min have been identified for a number of endocrine, physiological and behavioral processes (Lloyd and Rossi, 1992). The functional significance of most of these rhythms is still unknown. However, based on the early findings of Knobil and Hotchkiss (1985), the crucial role of pulsatile hormone secretion has been recognized for the endocrine reproductive system and has led to important therapeutic applications.

In man, one of the most prominent ultradian rhythms is the regular occurrence of the two basic states of sleep: non-rapid-eye movement (NREM) sleep and REM sleep which alternate with an 80–120 min period. Using electroencephalographic (EEG) spectral analysis, which provides a dynamic description of sleep processes, certain authors have reported that the delta wave activity (0.5–3.5 Hz) characterizing the depth of sleep oscillates with a similar period (Aeschbach and Borbély, 1993). In addition to the homeostatic parameters of sleep, it is considered that the rhythmic occurrence of NREM-REM sleep cycles is a salient feature of good sleep quality. Poor sleep is attributed to irregular and fragmented sleep cycles.

Using either time or frequency domain indexes of heart rate variability, many of studies have reported that REM sleep is characterized by a larger heart rate variability than NREM sleep. In particular, the standard deviation of normal R-R intervals reflecting the overall heart rate variability is higher during REM sleep (Zemaitytë et al., 1984; Pivik et al., 1996). REM sleep also has been associated with an increased ratio of low to high frequency power (LF/HF) calculated by spectral analysis of R-R intervals, which is thought to reflect sympathovagal activity (Berlad et al., 1993; Baharav et al., 1995; Vanoli et al., 1995; Vaughn et al., 1995; Bonnet and Arand, 1997). In recent years, heart rate variability has been investigated in relationship with different EEG frequency bands, in particular with alpha activity (Ehrhart et al., 2000), with theta activity (Rowe et al., 1999), and with the cyclic alternating pattern (CAP)

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1388-2457/01/$ - see front matter 
CLINPH 2000799
PII: S1388-2457(01)00507-7

which consists of arousal-related phasic events that periodically interrupt the tonic theta-delta activities of NREM sleep (Ferri et al., 2000; Ferini-Strambi et al., 2000).

In previous studies (Otzenberger et al., 1997, 1998), we found that the nocturnal profiles of the LF/HF ratio and of the autocorrelation coefficient of R-R intervals, a new marker of heart rate variability, were tightly coupled to the EEG mean frequency. We proposed also that low or decreasing levels in the LF/HF ratio are prerequisites for the increase in slow wave activity (Gronfier et al., 1999).

In the present study, we examine the concomitant profiles in delta wave activity and heart rate variability in good sleepers with regular NREM-REM sleep cycles and demonstrate the existence of regular oscillations in heart rate variability tightly coupled to sleep stage alternation and inversely related to the oscillations in delta wave activity.

## 2. Methods

### 2.1. Subjects and protocol

Nine subjects who had regular 80–120 min NREM-REM sleep cycles and who reported at the end of the night a subjective assessment of good sleep quality were included in the study. All the subjects (20–30 years old) were in good health and had no history of cardiovascular or other disease or drug use. None of the subjects was taking any form of medication. The protocol was approved by the Hospital Ethics Committee and all subjects gave their written informed consent to participate in the study. The experiments were carried out in a soundproofed, air-conditioned sleep room. After 1 night of habituation, the subjects underwent 1 night-long experimental session during which sleep and cardiac recordings were made. Electrodes for polysomnographic and electrocardiographic (ECG) recordings were applied at 20:00 h. The subjects were supine from 21:00 h to 09:00 h, the lights were switched off from 23:00 to 07:00 h, and the subjects were awakened at 07:00 h. Fifteen minutes after awakening, sleep quality was assessed by a questionnaire (Akerstedt et al., 1994).

### 2.2. Sleep analysis

Sleep recordings were taken from 23:00 to 07:00 h with a sampling frequency of 256 Hz using an Astro-Med EEG system (Grass Instrument, Rhode Island, USA). Four EEG (F3, C3, P3 vs A2 and C4 vs A1), one chin electromyogram (EMG) and one electrooculogram (EOG) were recorded. They were visually scored at 30-s intervals using standardized criteria (Rechtschaffen and Kales, 1968). For all-night spectral analysis, which provides a dynamic description of the sleep EEG, the EEG signal (C3-A2 or C4-A1) was high-pass (0.5 Hz) and low-pass (35 Hz) filtered before being analog to digital converted. Artifacts were visually detected, and periods overlapping with artifacts were discarded from further analysis. Absolute power spectra were computed for consecutive 2-s periods using a fast Fourier transform algorithm. Data were then averaged to yield a median estimation every 5 min. The spectral parameter studied was the absolute power in the delta frequency band (0.5–3.5 Hz).

### 2.3. Heart rate analysis

The ECG was recorded from 21:00 to 09:00 h using the Astro-Med EEG system. The R-R intervals, i.e. the length of time between the R peaks of consecutive QRS complexes, were calculated and checked for artifacts. Occasional ectopic beats were identified and replaced with interpolative R-R interval data. Power spectral analysis of each consecutive 5-min recording was performed sequentially with a fast Fourier transform based on a non-parametric algorithm using a Welsh window, after the ectopic-free data were detrended and resampled. A fixed resampling frequency of 1024 equally-spaced points in 5-min periods was used. The power densities in the LF band (0.04–0.15 Hz) and in the HF band (0.15–0.50 Hz) were calculated for each 5-min density spectrum by integrating the spectral power density in the respective frequency bands. The LF/(LF + HF) ratio was then calculated.

### 2.4. Statistical analysis

To identify the dominating frequency underlying the oscillations in the delta wave activity and in the LF/(LF + HF) ratio, spectral analysis was performed on individual profiles. The period having the highest spectral density was identified, and its significance was checked using Hartley's test (Priestly, 1981). The temporal link between the overnight profiles in delta wave activity and the LF/(LF + HF) ratio was quantified using cross-correlation analysis for lags $-2$ to $+2$, each lag corresponding to a 5-min interval. The highest cross-correlation coefficient was then identified with its level of significance. The association between individual oscillations of delta wave activity and LF/(LF + HF) ratio was tested for by a lagged coincidence analysis based on a model of a conditional probability as proposed by Veldhuis et al. (1991). To establish the mean profiles in the 9 good sleepers, the individual differences in the duration of the sleep episodes were normalized according to a method derived from Achermann et al. (1993). Individual data in sleep stage 2, slow wave sleep (SWS), and REM sleep episodes from the first 4 NREM-REM sleep cycles were subdivided into equal parts. Data were then averaged over subjects, and the standard error (SE) was calculated for each 5-min interval. Mean changes in delta wave activity and LF/(LF + HF) in each NREM-REM sleep cycle were analyzed by one-way ANOVA for repeated measurements with time as a factor. Results are expressed in percentages of the mean overnight values. The difference was considered to be significant when $P < 0.05$.

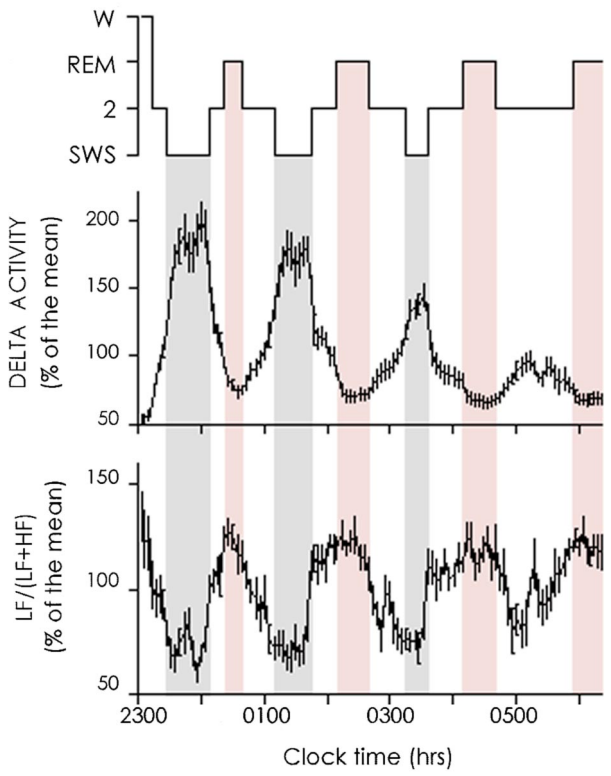


Fig. 1. Mean (±SE) normalized profiles of delta wave activity and LF/(LF + HF) ratio together with the hypnogram. LF/(LF + HF), ratio of low frequency (LF) to LF + high frequency (HF), calculated from spectral analysis of R-R intervals. W, wake; REM, rapid eye movement sleep; SWS, slow wave sleep. SWS lies in the gray areas and REM sleep in the pink areas. Values are expressed as percentages of the mean overnight values of each subject. The *x*-axis gives the real time of sleep episodes averaged for 9 subjects over the first 4 NREM-REM sleep cycles.

## 3. Results

Fig. 1 illustrates 5-min nighttime profiles in delta wave activity and in the LF/(LF + HF) ratio in the 9 good sleepers with regular NREM-REM sleep cycles, together with the mean normalized hypnogram. In each NREM-REM sleep cycle, the delta wave activity and the LF/(LF + HF) ratio showed significant inverse oscillations ($P < 10-^5$). The LF component had a predominant part in the variations of the LF/(LF + HF) ratio, with significant ($P < 10-^5$) decreases during each NREM-REM sleep cycle throughout the night. In contrast, the HF component was slightly but significantly ($P < 0.01$) decreased only during the first NREM-REM sleep cycle. Coincidence analysis revealed that peaks of delta wave activity were preceded by troughs in the LF/(LF + HF) ratio by $-5 \pm 5$ min ($P < 10-^5$), and that the onsets of the oscillations in delta wave activity were preceded by the onsets of the inverse oscillations in the LF/(LF + HF) ratio with the same time lag ($10 - ^5$). Overnight cross-correlation between the profiles in delta wave activity and in LF/(LF + HF) confirmed this phase advance, with the highest coefficients observed in all individuals at $-5$ min ($-0.382$ to $-0.734$; $P < 0.001$), indicating that cardiac changes preceded EEG changes by about 5 min. To investigate the regularity of the oscillations and to identify the dominant frequency underlying them, spectral analysis was performed on individual profiles. The periodicities for both delta wave activity and the LF/(LF + HF) ratio ranged between 80 and 120 min among the subjects ($P < 0.001$).

Normalizing the individual hypnograms allowed pure stage 2, REM sleep and SWS to be averaged and characterized. We confirmed that during SWS, the LF/(LF + HF) ratio was the lowest, and that during REM sleep, the highest. There was a duality in sleep stage 2, which became progressively quieter with a decrease in the LF/(LF + HF) ratio from REM sleep to SWS. During the transition from SWS to REM sleep, sleep stage 2 was characterized by an abrupt increase in the LF/(LF + HF) ratio concomitant to the micro-arousals that generally terminate SWS. The LF/(LF + HF) ratio remained as high during sleep stage 2 as during the subsequent REM sleep episode, and decreased again at the end of REM sleep before the next SWS episode (Fig. 1). Individual profiles revealed large increases in the LF/(LF + HF) ratio in each short-term transition from deeper sleep to lighter sleep.

## 4. Discussion

These results revealed the existence of ultradian oscillations in heart rate variability linked in a ‘mirror-image’ to the overnight oscillations in delta wave activity. Interestingly, cardiac changes preceded EEG activity by about 5 min. Sleep stage 2 represents a ‘pivot’, with progressively decreasing levels in the LF/(LF + HF) ratio during the transition from REM sleep to SWS, and conversely, with an abruptly increasing ratio from SWS to REM sleep. Heart rate variability oscillates then during the whole night from low levels during SWS to high levels coinciding with the microarousals that generally terminate SWS and which persist during the subsequent sleep stage 2 and REM sleep.

A large number of studies have linked changes in heart rate variability during the different sleep stages to underlying autonomic nervous activity (Baharav et al., 1995; Berlad et al., 1993; Vanoli et al., 1995; Vaughn et al., 1995; Bonnet and Arand, 1997). In particular, spectral power in HF areas, usually from 0.15 to 0.5 Hz, has been used to infer parasympathetic nervous system activity. The LF peak in the 0.04 to 0.15 Hz range has been related to predominant sympathetic influences, and the LF/HF ratio and the normalized LF/(LF + HF) ratio are commonly regarded as indexes of sympathovagal balance (Task Force, 1996; Malliani, 1999). It is then tempting to propose that there exists in good sleepers an oscillatory process in sympathovagal balance that adjusts in anticipation to sleep-stage alternation and underlies the sleep-stage related changes in cardiovascular or thermoregulatory responses seen in other studies (Somers et al., 1993; Lavie et al.,

2000; Liguori et al., 2000). However, there are a number of recent studies demonstrating that the LF/HF ratio does not accurately reflect changes in sympathovagal balance (Eckberg, 1997; Houle and Billman, 1999). Therefore, even if this subject is still a matter of debate (Malliani, 1999) and also because heart rate variability is influenced by changes in respiratory frequency that occur during the alternation of NREM-REM sleep (Brown et al., 1993), care should taken in relating the present data on heart rate variability to the activity of the autonomic nervous system.

Nevertheless, the results presented here are of interest because they reveal an oscillatory process in heart rate variability during sleep which has not been described in other physiological conditions. The strong coupling between cardiac and EEG activities suggests that there are common pathways between the central autonomic network that controls cardiovascular responses (Benarroch, 1993; Dampney, 1994) and the neurons with their activity modulated by noradrenergic neurotransmitters acting as 'REM-off' and 'REM-on' factors (McCarley and Massaquoi, 1992) or as sleep-promoting and sleep-wake switch factors (Gallopin et al., 2000; McGinty and Szymusiak, 2000).

For endocrine system too, such oscillatory profiles have been reported during sleep. For example, renin (Luthringer et al., 1995), cortisol (Gronfier et al., 1998), and thyreostimuline (Gronfier et al., 1995) have been found to be temporally linked to oscillations in delta wave activity. In this context, it should be mentioned that no sleep-stage related variations could be found for noradrenaline measured every 10 min in 4 subjects (unpublished observations). Taken together, these results suggest that common central mechanisms may be involved in the harmonious coordination of ultradian processes that ensure good sleep quality. This study opens then a new field of research aimed at determining the functional connections among the ultradian rhythms in endocrine, cardiac and EEG activities.

## Acknowledgements

The authors would like to thank S. Zahn, D. Joly and M. Siméoni for experimental assistance and data treatment. We thank Dr J.M. Pequignot and J.M. Cottet-Emard (Laboratoire de Physiologie de l'Environnement, Lyon, France) for noradrenaline measurements.

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