Medical Infobahn for Europe
A. Hasman et al. (Eds.)
IOS Press, 2000

Heart rate Variability During Sleep Stages in Normals and in Patients with Sleep Apnea

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Abstract. Heart rate and heart rate variability are under the control of the autonomous nervous system. It can be assumed that during sleep internal influences dominate the autonomous nervous system. During the different sleep stages heart rate regulation differs in normal subjects. Obstructive sleep apnea is a disorder which has its origin in sleep and has strong modulating effects on the autonomous nervous system with prominent heart rate variations in consequence. In order to separate the influences of sleep stages and sleep apnea on heart rate variability we applied detrended fluctuation analysis in 12 healthy subjects and 20 patients with sleep apnea. We could show that the differences between sleep stages observed in healthy subjects were still present in subjects with sleep apnea despite their cyclical variation in heart rate. We conclude, that detrended fluctuation analysis is able to separate the influences of sleep stages and sleep apnea on heart rate variability.

1. Introduction

Heart rate and heart rate variability during sleep are under the control of the autonomous nervous system. Today it has been recognized that many different disorders originate during sleep causing daytime symptoms like excessive daytime sleepiness. Sleep-related breathing disorders with repetitive cessations of respiratory airflow and concomitant drops in oxygen saturation have a prevalence of 4% in males and 2% in females within the age of 30 to 60 years [1]. Obstructive sleep apnea is the most well-known manifestation of sleep-related breathing disorders. Sleep apnea is characterized by repetitive pauses in respiratory flow of at least 10 seconds which can occur up to 600 times in one night. The respiratory pauses are caused by a collapse of the upper airways when muscle tone drops during falling asleep. Each single apnea is followed by a central nervous activation, triggered by the lowered oxygen saturation and resulting in a stabilization of the upper airways for a few successful breaths. The so called arousals prevent the patient from coming to deep sleep and in consequence disturb the recreative function of normal sleep. In addition the repetitive apneas are accompanied by a pronounced increased variation in heart rate which is strong enough to support diagnosis. The characteristic pattern found is called "cyclic variation of heart rate" [2]. During each apnea a relative bradycardia is found and the arousal which is a an activation of sympathetic tone is accompanied by an sudden increase in heart rate.

Investigations of the physiology of the heart beat did show, that heart rate and heart rate variations are strongly dependent on sleep stages [3, 4]. Both influences modulate heart rate variability in these patients. Earlier investigations tried to apply spectral analysis to heart rate in order to quantify influences on heart rate with periodic behavior [3, 5].

2. Methods

2.1 Sleep recordings

Sleep recordings were performed using established criteria. We recorded two leads of EEG, two leads of EOG, the EMG submentalis, EMG tibialis, ECG, oronasal airflow, thoracic and abdominal respiratory movements (Respitrace), oxygen saturation (Nellcor pulse oximeter), snoring and body position. All sleep recordings were attended by experienced technicians which took care of the patients and electrodes during the night. We recorded at least eight continuous hours from 22:00 to 06:00. Data were recorded digital with 200 Hz sampling rate for the ECG and EEG and with 16 bit resolution. Respiration and oxygen saturation were digitized at sampling rates of 25 Hz. All signal data were stored in the European data format (EDF) [6], which allows easy exchange with other programs to display the signals and gives access to many analysis tools, such as sleep scoring.

Sleep stages were scored according to the rules of Rechtschaffen and Kales [7]. Respiration was scored for apneas, hypopneas and oxygen desaturations. Heart rate was calculated on the basis of R-R interval analysis using a QRS detection algorithm.

Analysis was done separately for patients with severe apnea (more than 40 phases per hour of sleep), mild apnea (less than 20 apneas per hour of sleep and healthy persons of different age. The groups were separated because heart rate variability in all different sleep stages was compared. Patients with severe sleep apnea no longer have slow-wave sleep as a consequence of severe sleep fragmentation.

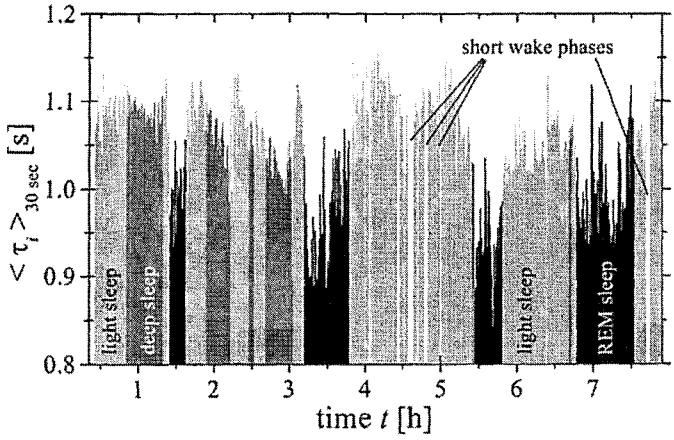

Figure 1: Heart beat intervals were plotted with sleep stages coded underneath the curve. Here R-R interval values are averaged over 30 seconds corresponding to the time resolution of sleep stages. The areas in black mark the REM sleep stage while light and dark gray have been chosen for light and deep sleep, respectively.

2.2 Analysis of heart rate

We investigated the correlation of subsequent inter-beat intervals τ_i with different time lags t by applying the detrended fluctuation analysis (DFA) [8, 9]. Quantitatively, the correlation in the τ_i can be characterized by the (auto)correlation function

$$C(t) = \langle \tau_i \, \tau_{i+t} \rangle = \frac{1}{T-t} \sum_{i=1}^{T-t} \tau_i \, \tau_{i+t} \,,$$

for a time series of total length T. If the τ_i are uncorrelated, $C(t)$ is zero for $t > 0$. For short-range correlations of the τ_i, $C(t)$ decays exponentially, and for long-range correlations, it decays as power-law,

$$C(t) \sim t^{-\gamma},$$

with an exponent $0 < \gamma < 1$. A direct calculation of $C(t)$ is hindered by the level of noise present in the finite heartbeat time series, and by non-stationarities in the data that are clearly seen in fig. 1. Therefore, we do not calculate $C(t)$ directly, but instead consider the interval profile [8]

$$Y(n) = \sum_{i=1}^{T} [\tau_i - \langle \tau_i \rangle],$$

where $\langle \tau_i \rangle$ denotes the average interbeat interval; see fig. 2. According to random walk theory, the fluctuations $F(t)$ of the profile $Y(n)$ in a given time window of length t are related to the correlation function $C(t)$. To find how the fluctuations of $Y(n)$ scale with t, we divide the profile into T/t non-overlapping segments of size t; see fig. 2 for illustration. For linear DFA, we define the local trend for each segment s by a least-square linear fit. Then, we define the detrended profile, denoted by $Y_t(n)$, as the difference between the original profile and the linear fits,

$$Y_t(n) = Y(n) - a_s n - b_s .$$

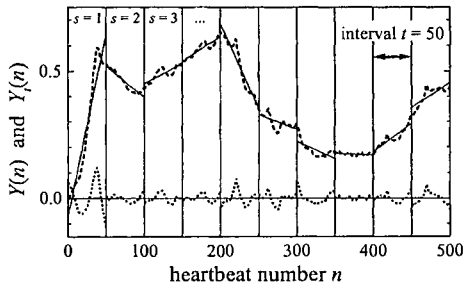

Figure 2: Illustration of the Detrended Fluctuation Analysis: The heartbeat interval profile $Y(n)$ (thick dashed line) is split into segments of size $t = 50$, and straight lines are fitted to the profile in each segment. The deviations $Y_t(n)$ from the fits (dotted line) determine the fluctuation function $F(t)$.

(compare fig. 2). For 2nd, 3rd and 4th order DFA, quadratic, cubic, and 4th order polynomials are used in the fitting procedure instead. Thus, higher order trends can be removed. Finally, we average the variance of the detrended profile over all n and take the square root,

$$F(t) = \left[\frac{1}{T} \sum_{n=1}^{T} Y_t^2(n) \right]^{1/2} .$$

It is apparent, that the variance will increase with increasing size t of the segments. For the relevant case of long-range power-law correlations, the fluctuations increase by a power law,

$$F(t) \sim t^{\alpha} \quad \text{with } \alpha = 1 - \gamma/2 .$$

Hence, by measuring the exponent α we can detect the correlation exponent γ. For uncorrelated data and short-range correlations, we have $\alpha = 1/2$, while $\alpha > 1/2$ signals long-

range correlations. Thus, the type of correlations present in the data can be determined by investigating the scaling behavior of $F(t)$.

We applied this method to heart rate time series gained from sleep recordings of 12 healthy subjects and 20 patients with moderate sleep apnea. For this analysis only patients with moderate sleep apnea with less than 20 apneas per hour of sleep were chosen, because patients with severe sleep apnea no longer have slow-wave sleep as a consequence of sleep fragmentation. Heart rate variability in all different sleep stages were compared.

3. Results

The correlation exponents α determined by DFA showed significant differences between sleep stages. In slow-wave sleep, only short-range correlations are present in the data. Using longer time lags than 10 sec, the correlations disappear, indicating a more "random" behavior. In light sleep a similar effect was found, but a loss of correlations occurred at larger times. In REM sleep, correlations remained large, even for longer time lags, at least up to 500 sec. This indicates the presence of heart rate regulating influences, similar to wakefulness in contrast to slow-wave sleep. When comparing these results for normal subjects with patients suffering from moderate sleep apnea, we found that the modulating influence of sleep stages on heart rate variability remained very strong even though obstructive sleep apnea caused additional variations. Only the crossover from the short-range correlated to the uncorrelated behavior in the non-REM stages was shifted to larger times. The additional fluctuations are directly linked with the disturbed respiration during sleep. The observed patterns typically show a cyclical variation of heart rate directly related to the repetitive events of apnea. Our analysis suggests that this typical pattern does not affect the underlying sleep stage-dependent heart rate variability to a great extend.

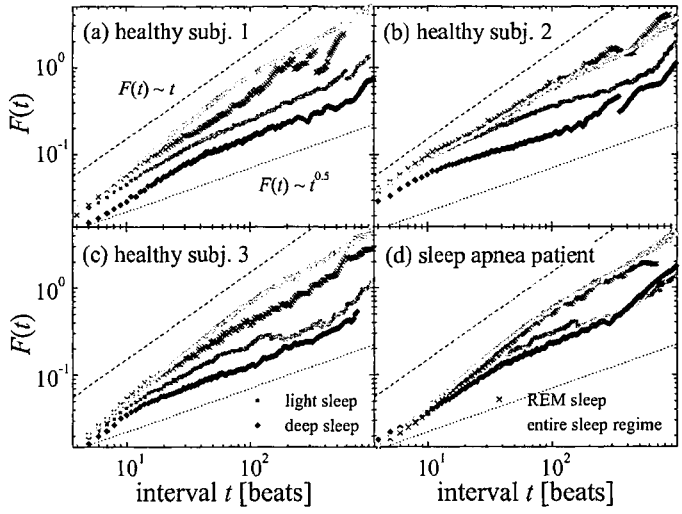

Figure 3: The results of the Detrended Fluctuation Analysis were plotted as the fluctuation function $F(t)$ over the intervals t for three healthy subjects (a-c) and one sleep apnea patient (d). The exponent α is the slope in the log-log plots. For $50 < t < 300$, α is close to 0.85 for REM sleep (crosses) indicating long-range correlations, while α is close to 0.5 for light and deep sleep (filled symbols) indicating the loss of correlations.

4. Discussion

The results of our study did confirm the known differences between statistical measures of heart rate in different sleep stages, as they have been reported [3, 4, 10]. The differences between of mean values in different sleep stages can be observed already in figure 1. The DFA was used to remove these systematic differences of mean heart rate in the sleep stages and to investigate the rules responsible for the variations independent of underlying trends. Statistical analysis of fluctuations then remained to be influenced by the transitions between sleep stages. Earlier studies also reported the effect of arousal on heart rate variability [10]. Therefore these transitions were also removed. Initially we wanted to separate sleep related breathing disorders after this preprocessing of the time series. To our surprise the differences in correlation behaviour found for different sleep stages remained to be the same in patients with sleep apnea and the differences between normal volunteers and patients with sleep apnea for individual sleep stages were small compared to the differences between the individual sleep stages.

5. Conclusion

Detrended analysis can remove short and long-term trends in heart rate. Thereby it is possible to study the mechanisms responsible for the variability of heart rate. Any studies on the variability of heart rate during sleep must consider and remove transitions between sleep stages because they are accompanied by movements which cause major variations in heart rate. After having removed trends and transitions we compared sleep stages in normals and patients with obstructive sleep apnea. Our results suggests that the typical pattern of cyclical variation of heart rate seen in patients with obstructive sleep apnea does not affect the underlying sleep stage-dependent heart rate regulation when compared to normal sleep.

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