Cardiovascular And Respiratory Dynamics in Patients With Sleep Apnea

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Abstract — Sleep is an active and regulated process with restorative functions for physical and mental conditions. Based on recordings of brain waves and the analysis of characteristic patterns and waveforms it is possible to distinguish wakefulness and five sleep stages. Sleep and the sleep stages modulate autonomous nervous system functions such as body temperature, respiration, blood pressure, and heart rate. Methods of statistical physics are used to analyze heart rate and respiration to detect changes of the autonomous nervous system during sleep. Detrended fluctuation analysis and synchronization analysis and their applications to heart rate and respiration during sleep in healthy subjects and patients with sleep disorders are presented. The observed changes can be used to distinguish sleep stages in healthy subjects as well as to differentiate normal and disturbed sleep on the basis of heart rate and respiration recordings without direct recording of brain waves. Of special interest are the cardiovascular consequences of disturbed sleep because they present a risk factor for cardiovascular disorders such as arterial hypertension, cardiac ischemia, sudden cardiac death, and stroke.

I. INTRODUCTION

SLEEP is not just the absence of wakefulness but has an own internal structure. The internal structure can be described by sleep stages that are differentiated based on typical patterns and waves found in the electroencephalography (EEG), electrooculography (EOG) and electromyography (EMG) recordings. The technique of sleep recording and the definition of sleep stages based on visual pattern classification was specified in guidelines compiled by Rechtschaffen and Kales (1968) [1]. These guidelines are used in clinical sleep medicine as the universal common language to describe normal and disturbed sleep. Beside wakefulness there are sleep stages S1 to S4 with an increasing depth of sleep. In addition to these REM sleep is defined. During 'REM sleep' EMG amplitude drops to its lowest values and the EEG reflecting brain activity is wake like. Characteristic for REM sleep are the rapid eye movements.

The sleep recording is labeled with these sleep stages in consecutive 30-second epochs based on a visual evaluation performed by sleep physicians or trained sleep technicians [1]. In normal sleep the stages follow a structured sequence starting with wake, then light sleep with stages 1 and 2, followed by deep sleep (slow wave sleep) with stages 3 and 4 and then followed by REM sleep. Such a sequence is called a sleep cycle and this has an average duration of 90 to 110 minutes. A normal night consists of 6 sleep cycles where the proportion of deep sleep decreases from the beginning to the end of the night and the proportion of REM sleep increases at the same time.

Sleep disorders comprise those with problems of insomnia and hypersonnia. Insomnia is characterized by problems to initiate and maintain sleep. Problems to start sleep, frequent awakenings or early morning wake-ups are common. As a consequence sleep is no longer restorative and daytime performance is impaired. Insomnia may be caused by stress, physical pain, drugs, substances or external disturbances. Hypersonnia appears to be the opposite in terms of patient complaints. Affected patients report of being sleepy all day long and having long sleep during the night with few awakenings. Nevertheless their sleep is also not restorative. Even with long sleep they are not recrested because they lack of deep sleep and REM sleep and the sequence of sleep stages may be disturbed heavily. Hypersonnia may be caused by sleep apnea, periodic legs movements, narcolepsy, drugs or substances. More than 80 particular sleep disorders are recognized and are defined by their specific pathophysiological conditions.

In order to distinguish the sleep disorders, to find the appropriate diagnosis and thereafter the adequate treatment, sleep laboratories perform cardiorespiratory sleep studies. Respiration is recorded with respiratory effort sensors at the chest and the abdomen, effective oro-nasal airflow with thermistor sensors or nasal pressure transducers, snoring with a laryngeal microphone and oxygen saturation derived from a finger or ear pulse oximetry. The electrocardiogram (ECG) is recorded using chest electrodes. The EMG of both legs is recorded to detect periodic movements of the limbs during sleep.

Manuscript received April 23, 2010. This work was supported in part by the German Research Foundation DFG under Grant BR 1303/8–1, KA 1676/3-1, KU 837/20–1, PE 628/3-1 and BR 1303/10–1, KU 837/23-1, PE 628/4-1.


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Sleep laboratories use computer based equipment with digital recording, evaluation and archiving of the above mentioned biological signals. The evaluation of sleep is still based on visual inspection of all these signals because automatic analysis of sleep recordings has still many limitations in terms of accuracy and sensitivity and therefore has not been accepted by sleep physicians.

II. OBSTRUCTIVE SLEEP APNEA

Obstructive sleep apnea is a sleep disorder characterized by repetitive cessations of respiratory flow for at least 10 seconds. Typically sleep apnea events last for 30 to 60 seconds. The respiratory cessations are due to a collapse of the upper airways which are normally kept open during breathing. With the drop of muscular tone during the period of falling asleep in patients with sleep apnea there is a faster drop in muscular tone of the upper airways than the diaphragm and the accessory respiratory muscles. Thus with a continued muscular effort of breathing during sleep the upper airways collapse when the negative intrathoracic pressure created for inspiration during each breath becomes too strong to keep the upper airways open. Each apnea ends with a central nervous activation (arousal) which reconstitutes the regulation of breathing. The arousal is caused by the drop in oxygen and the increase in carbon dioxide during the course of the apnea. These arousals remain below the level of wakefulness and are not noticed by the patient affected by sleep apnea. A patient with sleep apnea may have 400 single apnea events in one night. Not always the upper airway obstruction needs to be complete. A partial obstruction is called hypopnea. The average number of apnea and hypopnea events related on the hour of sleep after subtracting all wake times is called the apnea-hypopnea index (AHI). This number is used for the definition whether a patient suffers from sleep apnea, hereby meaning the sleep disorder. If the AHI is above 5 accompanied with additional hypersomnia as reported by the patient or if a patient has an AHI above 15 based on the evaluation of cardiorespiratory polysonomography then the diagnosis of sleep apnea is taken by the sleep physician.

Cardiovascular changes accompany every single apnea event. With each apnea the heart rate decreases. During the apnea we do see a relative bradycardia. After the end of the apnea when respiration reconstitutes a relative tachycardia is observed. Blood pressure decreases during the apnea and increases near the end of the apnea as the sympathetic tone increases. During the few breaths enormous increases in blood pressure were observed. Oxygen saturation drops with the cessation of respiration and reaches its nadir during the few resuscitating breaths. Swings in oxygen saturation and heart rate are so characteristic, that they have been used for early detection of sleep apnea with portable diagnostic devices.

The leading symptom in patients with sleep apnea is hypersomnia with the complaint of excessive daytime sleepiness. Excessive daytime sleepiness is the consequence of severe sleep fragmentation caused by the repetitive arousal during sleep. Even if the arousals remain below the level of consciousness, the temporal sequence of sleep stages is severely disrupted and the restorative function of sleep is destroyed. Sleep apnea is recognized as an independent risk factor for systemic hypertension.

Sleep apnea can be treated easily by applying a simple physical method. A continuous positive airway pressure (CPAP) applied through the nose using a tight mask increases the air pressure inside the upper airways. Thus the upper airways are prevented from collapsing when the muscular tone drops during the period of falling asleep. The apneas disappear, the cardiovascular changes disappear and the sleep fragmentation is reversed. Studies on the treatment effect of CPAP could prove a reversal of daytime sleepiness and of arterial hypertension even during daytime. This pneumatic method has to be used continuously and regularly during each night with sleep. If the CPAP is not taken, the apneas reappear immediately and also the sleep fragmentation comes back quickly. Sleep apnea can be regarded as a model disorder for sleep fragmentation and cardiovascular activation during sleep.

III. HEART RATE VARIABILITY

In order to find out how sleep and more particularly different sleep stages affect the autonomous nervous system, we investigated two of its representative signals: heart rate and respiration. The recording of the ECG has become standard for sleep recordings. The current evaluation is limited to simple statistics of heart rate variability (HRV) and a rough estimate of nocturnal arrhythmias. A diagnosis of arrhythmias requires the recording of more than one ECG lead as used in sleep recordings. The autonomous nervous system changes with sleep. Heart rate, blood pressure and respiratory rate are lowered to adapt to the reduced metabolic needs during normal sleep. Consequently mean heart rate values drop from wakefulness to light sleep and further to deep sleep. During REM sleep heart rate increases again showing a high variability which may exceed the variability observed during quiet wakefulness. Heart rate variability has been investigated using spectral analysis in order to derive sympathetic and parasympathetic activity being attributed to specific frequency ranges [3]. Using this analysis sleep stage specific changes of autonomic activities were identified. The spectral analysis had also been applied to sleep apnea subjects. One study showed that the characteristic pattern of bradycardia and tachycardia could be attributed to an effective parasympathetic control of heart rate interrupted by sympathetic activation at the apnea terminating arousal [4].

For the analysis of heart rate variability based on the ECG recording series of beat-to-beat intervals RRI, were calculated, disregarding artifacts and ectopic beats. Then the detrended fluctuation analysis (DFA) was applied. The DFA method [5] has become a widely-used technique for the
determination of the scaling properties and the detection of long-range correlations in noisy time series with trends. We studied the data of 14 normal volunteers and 64 sleep apnea patients [6, 7]. The DFA method was separately applied to the data recorded during wakefulness, REM sleep, light sleep, and deep sleep. In the method, the records are further divided into segments of length \( t \), and the variance of the data from polynomial fits in the segments is calculated for different segment sizes \( t \). Here, we used the DFA3 method for beat-to-beat interval data, where cubic polynomials are employed in this detrending procedure. The average variance defines the fluctuation function \( F(t) \), which is often found to scale as a power law,

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F(t) \sim t^\alpha
\]

In a double logarithmic plot we can draw \( F(t) \) over the time interval \( t \) and obtain \( \alpha \) as the slope of the resulting curve. If \( \alpha \) has values near 0.5 then we speak of uncorrelated beat-to-beat intervals or short-range correlations. If \( F(t) \) shows power-law scaling with \( \alpha \) significantly larger than 0.5 for large segment sizes \( t \) we speak of long-range correlations between beat-to-beat intervals. Here we used \( t \) values between 70 and 300 heartbeats to study the scaling behavior and determined the slopes alpha for each sleep stage and each subject by linear fits in double logarithmic plots.

Remarkable differences previously reported between day and night were also found between deep sleep, light sleep, REM sleep, and wakefulness within the sleep time [5]. This finding was consistent over all subjects being investigated. For the healthy subjects we found almost no long-range correlations during deep sleep (\( \alpha = 0.524 \pm 0.055 \pm 0.031 \); the first error interval indicates the average error of the slope for each subject; the second error interval indicates the fluctuation of the alpha values among the subjects, i.e., the standard deviation of the mean). On the contrary, there are clear long-range correlations during REM sleep (\( \alpha = 0.777 \pm 0.064 \pm 0.055 \), probability \( p < 0.001 \) for equivalence with deep sleep), almost similar to wakefulness (\( \alpha = 0.902 \pm 0.082 \pm 0.055 \), not significantly different from REM sleep). Light sleep (\( \alpha = 0.561 \pm 0.038 \pm 0.030 \)) was found to be very close to deep sleep.

Surprisingly, the result remained almost the same in patients with obstructive sleep apnea. Again there were almost no long-range correlations in deep sleep (\( \alpha = 0.538 \pm 0.045 \pm 0.035 \)) and light sleep (\( \alpha = 0.431 \pm 0.039 \pm 0.016 \)) but marked long-range correlations in REM sleep (\( \alpha = 0.848 \pm 0.060 \pm 0.033 \), probability \( p < 0.0001 \) for equivalence with deep sleep) which were similar to wakefulness (\( \alpha = 0.898 \pm 0.061 \pm 0.024 \)). Despite these similarities in the long-term correlations, there are also remarkable differences on shorter time scales, which have even been used for the detection of apnea events. The observed crossover time scale of about 50 heartbeats corresponds to the transitions between apneas and apnea-free time. Hence the crossover is due to the corresponding quasi-periodic variation; see for the effects of periodicitities on DFA studies.

Similar differences between REM sleep and wake periods on the one hand and non-REM sleep (light and deep sleep) on the other hand were found in the fluctuations scaling behavior of series of the signs sign (delta RRI) and amplitudes (magnitudes) \( |\Delta RRI| \) of the RR intervals increments delta RRI = RRI \( i \) − RRI \( i-1 \). In particular, the sign exponent varies from \( \approx 0.0 \) (non-REM sleep) to 0.3 (REM sleep and wake), while the amplitude exponent varies from \( \approx 0.5 \) (non-REM) to 0.7 (REM sleep and wake). The differences in the scaling behavior of the amplitudes shows that not only the linear scaling properties of heartbeat dynamics but also the nonlinear properties change across sleep stages, wake and sleep state, with the degree of nonlinearity gradually increasing from deep sleep, to light sleep to REM and to wake state. A stochastic modeling approach was shown to reproduce all these differences between the sleep stages as well as the scaling behavior for the full night with just two parameters.

Regarding the long-term correlations the differences between healthy and sleep apnea subjects were much smaller than the differences between sleep stages [7]. This indicates that the basic long-term mechanisms for heart rate control on a beat-to-beat level did not change very much with sleep apnea. We assume that this basic mechanism is strongly controlled by sleep stages. It seems likely that the long-range correlations during wakefulness and REM sleep are caused by the enhanced influence of the brain on the autonomous nervous system. When this influence is strongly reduced, as is the case during light sleep and deep sleep, the heartbeat intervals behave in a more random fashion. We note that long-term correlations both during wakefulness and REM sleep are also affected by the circadian pacemaker. However, the variation caused by the circadian system occurs on longer time scales (several hours) and it is much weaker (deviations from the mean remain below about 5 percent).

IV. Respiration Variability

In general human respiration is highly variable. Respiratory timing is characterized by the total time per breath \( T_{\text{tot}} \) and the inspiration time \( T_i \). We also study time series of respiratory volume such as the volume inhaled with each breath \( V_i \) [8]. To investigate the fluctuations these parameters must be measured on a breath-to-breath basis. This can be achieved by pneumotachography which is a quantitative measure of airflow. Since this method needs a full face mask covering nose and mouth, which is not very comfortable, only very few long-term studies have been performed so far.

As demonstrated earlier breath-to-breath variables are not purely random in resting awake humans, but characterized by a breath-to-breath coupling or short-term correlation. Moreover, some studies using autocorrelation analysis have shown that breath-to-breath correlations can increase with respiratory stimuli in wakefulness as well as in patients with
restrictive lung disease which are characterized by smaller lung volumes. As an interpretation of these data it has been suggested that the random variability of respiratory variables may be a measure of unconstrained influenced control, whereas the correlation may represent a more constrained automatic influenced control caused by an input from external or internal stimuli. To our knowledge during sleep a detailed breath-to-breathe analysis on constancy and random vs. nonrandom behavior of respiration and its regulation over long time series has not been presented before, although for REM sleep a rapid, irregular and for NREM sleep a very regular breathing pattern was reported.

Higher variability of breathing during rapid eye movement sleep than during non-REM sleep result from a complex regulation of respiratory timing and drive components. Breath-to-breath correlations may help to distinguish between nonrandom and random variability, respectively, which represent a more constraint or unconstraint control. To analyze the behavior of respiratory control, we studied the long-term correlation behavior of respiratory drive \( (V_I/T_I) \) and timing \( (T_I/T_{Tot}) \) [8].

In our study 29 healthy subjects underwent a cardiorespiratory polysomnography with a pneumotachograph and a full-face mask to assess respiration during sleep [8]. We studied data with the DFA technique. Since trends are weaker and time series are shorter for breathing, smaller segments have to be considered. Hence, it is advantageous to use DFA2A with quadratic polynomials for detrending. We studied time scales \( t \) between 16 breaths and one quarter of the maximal duration of each type of sleep.

During non-REM sleep the long-term correlations of all respiratory variables were close to uncorrelated \( (0.54\pm0.09 \text{ for } T_I/T_{Tot} \text{ and } 0.55\pm0.10 \text{ for } V_I/T_I) \). In REM sleep a strongly correlated behavior was observed for \( V_I/T_I \) \( (0.80\pm0.14) \), breathing frequency \( (0.85\pm0.12) \) and expiratory time \( (0.86\pm0.14) \), whereas long-term correlations were weaker for \( T_I/T_{Tot} \) \( (0.70\pm0.11) \) and inspiratory time \( (0.76\pm0.11) \). Additional short-term correlations occur in \( V_I/T_I \) during sleep.

The changes found seem to be the expression of an altered autonomic control of respiration during REM sleep. Moreover, the irregular breathing pattern during REM sleep is nonrandom and the breath intervals are not completely independent of each other. In addition one can assume that the shorter and stronger correlations of respiratory drive demonstrate a strong automatic influenced control, whereas the long-term correlation of respiratory timing are the result of cortical influences in REM sleep.

V. CONCLUSIONS

The analysis of the autonomic nervous system during sleep by the investigation of heart rate variability and respiratory variability gives insight into the regulation of sleep. We found that, when the brain is very active as in the "dream"-REM stage, heart rate as well as respiration have long-term correlations, like in the wake phase. In contrast, in deep sleep correlations of the heart rate and of respiration vanish after a few seconds. For heart rate, these results have been reproduced by a stochastic model recently [see 2].

We compared the altered autonomic nervous system function in obstructive sleep apnea with the results for normal subjects based on heart rate variability analysis. We found that the differences between the sleep stages are much clearer than the differences between healthy and sleep apnea subjects. For heart rate this means that the basic control in the different sleep stages is very dominant. Obstructive sleep apnea introduces an additional variation on heart rate with a characteristic bradycardia and tachycardia pattern corresponding to each single apnea event, but leaves the basic autonomous nervous system regulation untouched.

Certainly not all patients with sleep disordered breathing suffer from the same degree of cardiovascular disorders. Until today it is not possible to distinguish those patients with sleep apnea which do develop arterial hypertension and congestive heart failure and those who do not. Using the new synchronization and modeling methods will enable us to evaluate the usefulness of new parameters for this risk prediction. This can be achieved by parameterization of the estimated transformations, e.g. via polynomial fitting.

Our studies support the view that there is a strong interaction between the central nervous sleep regulation and the autonomous nervous system regulation. Both systems interact and measurable parameters cannot be interpreted without the knowledge about the current state of the other system.

REFERENCES


