33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

Cardiovascular and Respiratory Regulation During Sleep in Patients With Sleep Apnea With and Without Hypertension

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***Abstract*— Sleep is a physiological process with an internal program of a number of well defined sleep stages and intermediate wakefulness periods. The sleep stages do modulate the autonomous nervous system and thereby the sleep stages are accompanied by different regulation regimes for the cardiovascular and respiratory system. The differences in regulation can be distinguished by new analysis techniques on the recorded signals.**

In addition to normal sleep regulation some sleep disorders affect the cardiovascular and respiratory regulation. The most prevalent disorder linked to sleep and changes in the autonomous system is obstructive sleep apnea. In patients with obstructive sleep apnea marked short term changes in cardiovascular and respiratory regulation are observed during sleep. These abnormalities in regulation are further differentiated between the sleep stages. For long term changes obstructive sleep apnea is recognized as a major risk factor for arterial hypertension. Treatment of obstructive sleep apnea lowers blood pressure during the night and over time also lowers blood pressure during daytime.

In this study we investigated 18 patients with sleep apnea and normal blood pressure, 10 patients with sleep apnea and arterial hypertension and 10 normal subjects as controls. Both patient groups were tested with cardiorespiratory polysomnography before and under CPAP therapy. The effects on cardiovascular and respiratory regulation during sleep and daytime are investigated in the three groups.

Manuscript received March 26, 2011. This work was supported in part by the German Science Foundation under Grant DFG KU837/23-1, DFG PE 628/4-1 and BR 1303/10-1. Major parts of this study had been published recently in A. Suhrbier, M. Riedl, H. Malberg, T. Penzel, G. Bretthauer, J. Kurths, N. Wessel. Cardiovascular regulation during sleep quantified by symbolic coupling traces. Chaos 20, 045124 (2010).

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I. Introduction

DIRECTIONAL coupling analysis of bivariate time series is an important topic in current biomedical signal analysis. We use a method based on symbolic dynamics for detection of time-delayed coupling of time series during sleep in patients with obstructive sleep apnea. More specifically we apply this analysis to the coupling between heart rate and systolic blood pressure [1]. This is of high interest because we know that heart rate and blood pressure are modulated by sleep stages and by sleep pathologies. Obstructive sleep apnea is a major risk factor for arterial hypertension. With each single apnea event we see changes in heart rate and arterial blood pressure during the night. These changes are the consequence of multiple effects and these are seen in Fig. 1.

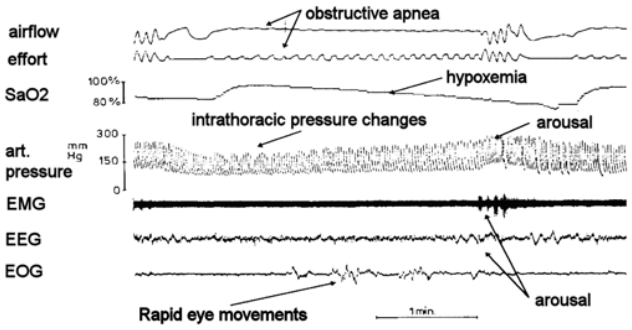

Fig. 1. The recording of one long obstructive apnea / hypopnea event is shown together with all influences on arterial blood pressure [2]. The obstructive apnea is characterized by a cessation of airflow. In addition we see respiratory effort movements which makes the event an obstructive one. Parallel with obstructive efforts we see small variations in systolic blood pressure. They are caused by intrathoracic pressure changes and are also called pulsus paradoxus. The drop in oxygen leads to hypoxemia. Parallel with hypoxemia we observe an increase in arterial blood pressure. At the end of the apnea event we see an arousal in the EEG and the EMG with a parallel strong increase in blood pressure. Systolic values above 220 mmHg are often observed. At the time of high blood pressure we can observe also cardiac arrhythmias which are well reflected in the blood pressure curve. The lowest curve shows EOG and rapid eye movements which characterizes the entire period as REM sleep. The REM sleep is the reason for the very long duration of this apnea event. Also the REM sleep is the reason for a high level of blood pressure during the entire period.

Therefore in this study the coupling analysis is used to investigate characteristics in patients with sleep apnea. A conventional coupling analysis based on cross correlation techniques can only show associations and not directions of the coupling process. Only new techniques can show directions in addition. As can be seen in the figure 1 the associations have a direction [2]. Therefore a coupling analysis should also reveal the direction if time lags are involved. This is essential to study the causal relation between cortical arousal and autonomous nervous system arousal. This analysis of direction may reveal a better understanding on the underlying pathophysiological mechanisms of the apnea events itself and thereafter on the effects of treatment. The treatment of first choice is continuous positive pressure ventilation with CPAP devices [3]. This therapy is just a physical support of the collapsing upper airways. The positive pressure keeps the upper airways open so that normal breathing can be maintained even when the upper airways tend to collapse due to low muscle tone [4].

II. Methods

A. Patients

For the application of the symbolic coupling traces, we consider cardiorespiratory polysomnography in the sleep lab of 18 normotensive (NT) patients with an age of 44.6 +/- 7.6 years, body mass index BMI 30.2 +/- 2.9 kg/m^2, all male and 10 hypertensive (HT) patients with an age of 44.1 +/- 8.1 years, BMI 34.1 +/- 4.9 kg/m^2, all male, suffering from obstructive sleep apnea with a repetitive obstruction of the upper airways for more than 10 s. Patients were recorded during a diagnostic night (DD) and three months later during a treatment night with CPAP ventilation. In addition to this 10 healthy subjects were recorded as controls but in these no CPAP was applied. We consider the first 5 min of the largest undisturbed period of light sleep (LS), deep sleep (DS), rapid eye movement (REM), and the awake state (W) for each subject (see Table 1).

TABLE I
NUMBER OF DATA SETS FOR THE GROUPS

Subjects	Measurement	W	LS	DS	REM
Controls	DD	7	10	10	10
NT	DD	14	18	18	18
	CPAP	13	14	14	14
HT	DD	8	10	6	8
	CPAP	8	9	9	9

NT = normotensive patients, HT = hypertensive patients, DD = diagnostic night CPAP = treatment night, W = wake, LS = light sleep, DS = deep sleep, REM = rapid eye movement sleep.

The epochs for some stages were excluded due to artifacts (e.g., only nine hypertensive patients had 5 min of undisturbed LS during CPAP therapy). Additionally a control group of ten healthy controls with age 44.8 +/- 6.7 years, BMI 25.3 +/- 2.7 kg/m2, all male is examined for the diagnostic night only. Sleep and blood pressure were normal in these subjects according to health and sleep questionnaires and an physician investigation during daytime prior to the study.

Fig. 2. The patients were recorded with polysomnography and parallel non-invasive continuous blood pressure using a Portapres device. The Portapres device is demonstrated in this foto. With two finger cuffs continuous blood pressure is recorded. The sensing cuff switches every 30 minutes and gives the other finger time to relax. The measurement principle is based on a volume clamp technique.

B. Recording methods

The cardiorespiratory polysomnography recordings include electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), respiratory airflow, respiratory effort of thorax and abdomen, electrocardiogram (ECG), and continuous blood pressure curve with the Portapres device (see figure 2) [4]. EEG, EOG, and EMG are used to score the sleep into different sleep stages according to the guidelines of Rechtschaffen and Kales [5].

C. Analysis methods

For group specific results, the mean and standard deviation of parameters are calculated for each group. From the ECG signal (sampling rate of 1000 Hz) of these periods, the instance of the heartbeats is determined using appropriate algorithms [6]. Intervals between successive heartbeats (B_i) beat-to-beat intervals are calculated and artifacts caused by, e.g., premature beats were removed in B_i by means of an adaptive filter [7, 8]. The maximum blood pressure value in

each beat-to-beat interval is extracted from the continuous blood pressure.

For the bivariate coupling analysis we used SCT [9]. For this the time series of heart rate intervals and of blood pressure values are transformed into symbol sequences. Based on the symbol sequences word lengths are defined. These are used to calculate bivariate word distributions (see figure 3). More details on SCT analysis are given in the corresponding publication by Wessel [9]. Also classic cross correlation function, mutual information, and cross recurrence analysis are calculated for the differentiated signals as well in order to maintain the comparison to the SCT results. More details on the recurrence analysis are given in the corresponding publication by Wessel [9].

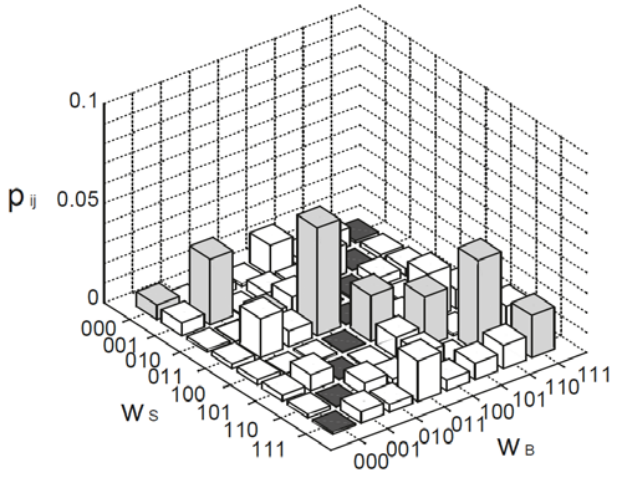

Fig. 3. Schematic illustration of the Symbolic Coupling Traces (SCT). Each diagonal of the bivariate word distribution represents symmetric and diametric behavior in the signals respectively.

For a better interpretation of the results, linear parameters of the beat-to-beat and blood pressure variability are considered. The mean value and standard deviation of time domain parameter as well as high frequency and low frequency components of the power spectra of the signals are considered. On one hand, the mean value is associated with the state of the cardiovascular system, which is mainly influenced by the long-term regulation of the neuroendocrine system. On the other hand, standard deviation as well as frequency components reflect the dynamics of the cardiovascular measurements. The power of the high frequency (HF) component, in the range of 0.15–0.4 Hz, reflects the respiratory influence as well as the very fast autonomic regulation via parasympathetic nervous system. The power of the low frequency (LF) component, in the range of 0.04–0.15 Hz, reflects the autonomic regulation of the antagonists parasympathetic and sympathetic nervous system.

This autonomic regulation of the opponent vegetative systems acts in the time range of hundreds of milliseconds to several seconds and is called short-term regulation. It is part of control loops which connect the cardiovascular measurements to each other. The baroreflex is a prominent example of this mechanism. It protects the body from sudden dramatical blood pressure changes by regulation of beat-to-beat intervals and peripheral resistance of the vessels and is quantified by the baroreflex sensitivity (BRS). BRS is estimated by means of sequence method where the slope of simultaneously rising of beat-to-beat intervals and blood pressure as well as falling is estimated. To quantify the influence of a 3 month CPAP therapy on the cardiovascular regulation, these standard parameters are compared before and after using the Kruskal–Wallis test.

III. Results

Considering the standard parameters, we obtain the following results. There are significant differences between the sleep stages in the parameters HF-S and LF-S in the normotensive DD group as well as in HF-B and LF-B in the hypertensive DD group ($p<0.05$, Kruskal–Wallis test). Interestingly, these differences are not present under CPAP therapy and in healthy controls, pointing to sleep disturbances such as snoring and/or apneas as the main cause for these differences. In the normotensive group, differences between the DD and the therapy CPAP night can be detected for HF-S in light and deep sleep as well as BRS in light sleep. For the normotensive group, differences are present for HF-S in light and deep sleep, for LF-B and LF-S in light sleep, as well as for BRS in deep sleep. Comparisons of patient groups with the control group show significant differences in HF-S, light and deep sleep (NT DD versus C), in HF-S, LF-S during REM (NT CPAP versus C), as well as in LF-S during light sleep and HF-S during REM (HT CPAP versus C).

The SCT results are compared to other standard methods such as R, I, and ΔRR by means of linear as well as nonlinear autoregressive models [9]. In contrast to previous publications [9], R and I are calculated also for differential time series to have a more appropriate comparison. Nevertheless, both parameters still have problems to detect time-delayed couplings in oscillating signals with noise interaction which results in additional coupling terms. In our data, we see R and I detecting too many lags, whereas the SCT and ΔRR consistently detect the lags 0 and 2. In addition, the SCT detects also lag +2 for that example of deep sleep.

IV. DISCUSSION

The time-delayed coupling analysis of the theoretical models and our measurements demonstrates the advantage of the SCT in comparison to standard methods. We confirm the results of [9] where SCT detects significant lags at $\tau = -2$ and $\tau = 0$ for all subjects. This strengthens the opinion about cardiovascular short-term regulation. The symmetric lag at $\tau = 0$ reflects the respiratory induced pressure and heart rate fluctuations, whereas the diametric lag at $\tau = -2$ represents the vagal feedback from B_i to S_i. We show that the coupling does not change in different sleep stages; however, the strength of interactions may differ. During deep sleep only, we see a loss of heart rate and blood pressure asymmetry as well as an effect of CPAP therapy on the cardiovascular coupling.

In this paper, we demonstrate that the SCT is more specific than the standard methods regarding the detection of delays and directions of interactions [1]. In [9] we applied the cross correlation, mutual information, and the cross recurrence analysis to the original simulated time series. Here we applied them, for a better comparability, to the differentiated time series and still obtain false lags. We assume these methods are more sensitive to non-stationarities, nonlinearities, and noise. Nevertheless, for the general assessment of coupling directions in time series, both new and established methods should be used. Coupling in stationary data with strong noise can be well detected via mutual information and cross correlation, whereas in deterministic data cross recurrence should be preferred. The parameters of the SCT method and cross recurrence based on order pattern close the gap in the coupling analysis of non-stationary time series with strong autocorrelation and moderate noise, where cross correlation, mutual information, and other methods are not sufficient to localize the lags exactly.

The opinion about the cardiovascular short term regulation is based on antagonistic nervous control via vagus and sympathicus. Here, we confirm the results of [9] with significant lags at $\tau = -2$ and $\tau = 0$. We show that this coupling pattern does not change in different sleep stages. The highest amplitudes for ΔT we find for deep sleep, the lowest for REM. This relation can be explained with a reduced sympathetic activity during deep sleep as quantified by LF-B leading to more pronounced respiratory influence and an increased vagal feedback. During deep sleep, where many physiological regulatory mechanisms are reduced we find an increased heart rate and blood pressure symmetry leading to multiple lags of $\tau = -2$ and $\tau = 0$.

Considering the CPAP therapy, we see that there are no different coupling patterns before and after treatment during the wake and the REM state. During deep sleep, we see differences in the cardiovascular couplings These results are confirmed by heart rate and blood pressure variability, mainly by HF-S, which reflects the mechanical effects of respiration on blood pressure: the higher the HF-S, the higher the respiratory effort [10]. The influence of the CPAP device on systolic blood pressure variations is obvious for all sleep stages, except wake. The baroreflex sensitivity shows no consistent effects for all sleep stages regarding the CPAP therapy. We see improvements during light sleep in the normotensive group and during deep sleep in the hypertensive group, similar to Bonsignore where mean BRS increased only slightly during CPAP application [11].

By comparing the significant differences in the standard parameters and the results of SCT analysis before and after CPAP therapy in light and deep sleep, we can conclude that the coupling information is independent of the variability parameters.

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