Cardiovascular Regulation During Sleep Quantified By Symbolic Coupling Traces

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Abstract

The different sleep stages modulate the autonomous functions blood pressure and heart rate as well as their complex interactions. The method of symbolic coupling traces (SCT) is used to analyse and quantify time-delayed couplings of these measurements. The SCT is defined by the difference of the symmetric and diametric traces of a bivariate word distribution matrix. It is applied to the signals of healthy controls as well as normo- and hypertensive patients with sleep apneas over night. We found significant different couplings not only between the deep sleep and the other sleep stages ($p<0.05$, Kruskal-Wallis test) but also between healthy subjects and patients. Thereby, SCT yields additional information which can not be measured by standard parameters of heart rate- and blood pressure variability. The proposed method may help to indicate pathological changes in cardiovascular regulation and also effects of continuous positive airway pressure therapy on the cardiovascular system.

1. Introduction

Sleep is a complex process which can be described by the series of passing sleep stages [1]. It is assumed that these sleep stages modulate the regulation of heart rate and blood pressure. The cardiovascular consequences of disturbed sleep are of particular high medical interest because they present a risk factor for cardiovascular disorders such as hypertension, and stroke.
The cardiovascular systems consist of several subsystems which are interrelated by feedback loops with time delay. Revealing such time delayed coupling directions is a basic task in understanding the system. Different methods, starting from cross correlation via mutual predictability to information-theoretic approaches are proposed for this purpose, but, due to the non-stationarity, nonlinearity, and the noise, the conclusions are not homogeneous.
In this paper, a method based on symbolic dynamics [2] for the detection of time-delayed coupling is presented for a more robust analysis of delayed coupling directions.

2. Methods

We consider polysomnographical measurements of 18 normotensive (NT, age: 44.6 ± 7.6 years, BMI: 30.2 ± 2.9 kg/m^2, all male) and 10 hypertensive patients (HT, age: 44.1 ± 8.1 years, BMI: 34.1 ± 4.9 kg/m^2, all male) suffering from obstructive sleep apnea syndrome (OSAS: repetitive obstruction of the upper airway for more then 10 seconds during sleep) during a diagnostic night (DD) and during treatment by means of continuous positive airway pressure (CPAP). For analysis, we select the first 5 minutes 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 Tab. 1). The epochs for some stages were excluded due to artefacts (e.g. only 9 hypertensive patients had 5 minutes of undisturbed LS during CPAP-therapy). Additionally, a control group of 10 healthy controls (C, age: 44.8 ± 6.7 years, BMI: 25.3 ± 2.7 kg/m^2, all male) is examined. The different sleep states are determined by the polysomnographical recordings using the protocol of Rechtschaffen and Kales [1]. From the electrocardiogram (sampling rate 1000 Hz), intervals between successive heart beats ($\{B_i\}$ - beat-to-beat-intervals) are determined [3]. Artifacts caused by, e.g., premature beats are removed by means of an adaptive filter [4]. Addition-

Table 1. Number of datasets for considered groups (C - healthy controls, NT - normotensive patients, HT - hypertensive patients, DD - differential diagnosis night, CPAP - night with CPAP therapy after 3 month CPAP treatment, W - awake state, LS - light sleep, DS - deep sleep, REM - rapid eye movement).

Subjects	Measurement	W	LS	DS	REM
C	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

ally, the maximum blood pressure value in each beat-to-beat interval ($\{S_i\}$ - systolic blood pressure) is extracted from the continuous blood pressure (via finger cuff of Portapres device mod. 2, BMI-TNO, Amsterdam, The Netherlands; sampling rate 200 Hz). For bivariate coupling analysis we used SCT [5]. First step of this approach is the transformation of B_i and S_i, into symbol sequences $s_B(t)$ and $s_S(t)$ according to the rule

$$s_z(t) = \begin{cases} 1 & z(t) \leq z(t+\theta) \\ 0 & z(t) > z(t+\theta) \end{cases} \quad (1)$$

where z represents B and S. For analysis of short-term couplings in B_i and S_i the value $\theta = 1$ has been used [5]. Next, words of length l are constructed $w_z(t) = s(t), s(t+1), ..., s(t+l-1)$ which can form $d = 2^l$ different patterns. For short-term dynamics in B_i and S_i, $l = 3$ is used to reliably estimate the bivariate word distribution [5]. $w_x(t)$ and $w_y(t)$ are used to calculate the bivariate word distribution $(p_{ij})_{i=1,...,d,j=1,...,d}(\tau)$

$$p_{ij}(\tau) = P(w_x(t) = W_i, w_y(t+\tau) = W_j) \quad (2)$$

with the d patterns W_1 to W_d. The parameter τ is included in order to consider delayed interrelationships between the signals. From the bivariate word distribution, the parameters

$$T = \sum_{i=j} p_{ij}(\tau) \quad (3)$$

$$\overline{T} = \sum_{i=1,...,d;j=d+1-i} p_{ij}(\tau) \quad (4)$$

$$\Delta T = T - \overline{T} \quad (5)$$

are calculated. On the one hand, T only captures influences which preserve the structure of the transmitted pattern of dynamics (symmetrical influences). On the other hand, $\overline{T}$ only quantifies influences which inverts the dynamical structure of the driver (diametrical influence). To answer the question if the parameter ΔT is significant or not, a critical value ΔT_{crit} is estimated respectively. Therefore, these parameters are calculated for 1000 realizations of bivariate white noise $N_i(0, \sigma^2)$ with sample length N. We look for the 99th percentile where 99% of the 1000 observation are smaller than that critical value. It represents the critical value of the significance level $\alpha = 0.01$ in an one-side significance test. The nonlinear regression leads to $\Delta T_{crit}(N) \approx \pm 2.7 \cdot N^{-0.51}$.
For a better interpretation of the results, linear parameters of the beat-to-beat and blood pressure variability are considered [6]. Mean value and standard deviation of time domain parameter as well as high frequency (HF: $0.15 < f < 0.4$Hz) and low frequency component (LF: $0.04 < f < 0.15$Hz) of the power spectra of the signals are considered. Additionaly, the influence of systolic blood pressure on beat-to-beat intervals is quantified by the baroreflex sensitivity (BRS). It 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 calculated [7]. To quantify the influence of a 3 month CPAP therapy on the cardiovascular regulation these standard parameters (partly shown in Tab. 2) are compared before and after using the Kruskal-Wallis test.

3. Results

The results of SCT and analysis of standard parameter of heart rate and blood pressure variability are presented in Fig. 1 and Tab. 2, respectively.

4. Discussion and conclusions

We confirm the results of [5] where SCT detects significant lags at $\tau = -2$ and $\tau = 0$ for all subjects. This strengthens the prevailing opinion about the cardiovascular short term regulation which is based on antagonistic nervous control via vagus and sympathicus. The symmetric lag at $\tau = 0$ reflects the respiratory induced arterial pressure and heart rate fluctuations, whereas the diametric lag at $\tau = -2$ represents the vagal feedback from B_i to S_i. Moreover, we show that this coupling pattern does not change generally in different sleep stages; however, the strength of interactions may differ. The highest amplitudes for ΔT we find for deep sleep, the lowest for REM (cf. Fig. 1). This relation can be explained with a reduced sympathetic activity during deep sleep as quantified by LF-B in Tab. 2 [9], leading to more pronounced respiratory influence and an increased vagal feedback. Again during deep sleep, where many physiological regulatory mechanisms such as cerebral blood flow and cerebral metabolic rate are reduced [10], we find an increased heart rate and blood pressure symmetry leading to multiple lags of $\tau = -2$ and $\tau = 0$. It shows a limitation of the coupling traces for symmetric oscillations, but this is a limitation of all methods for the detection of coupling directions.

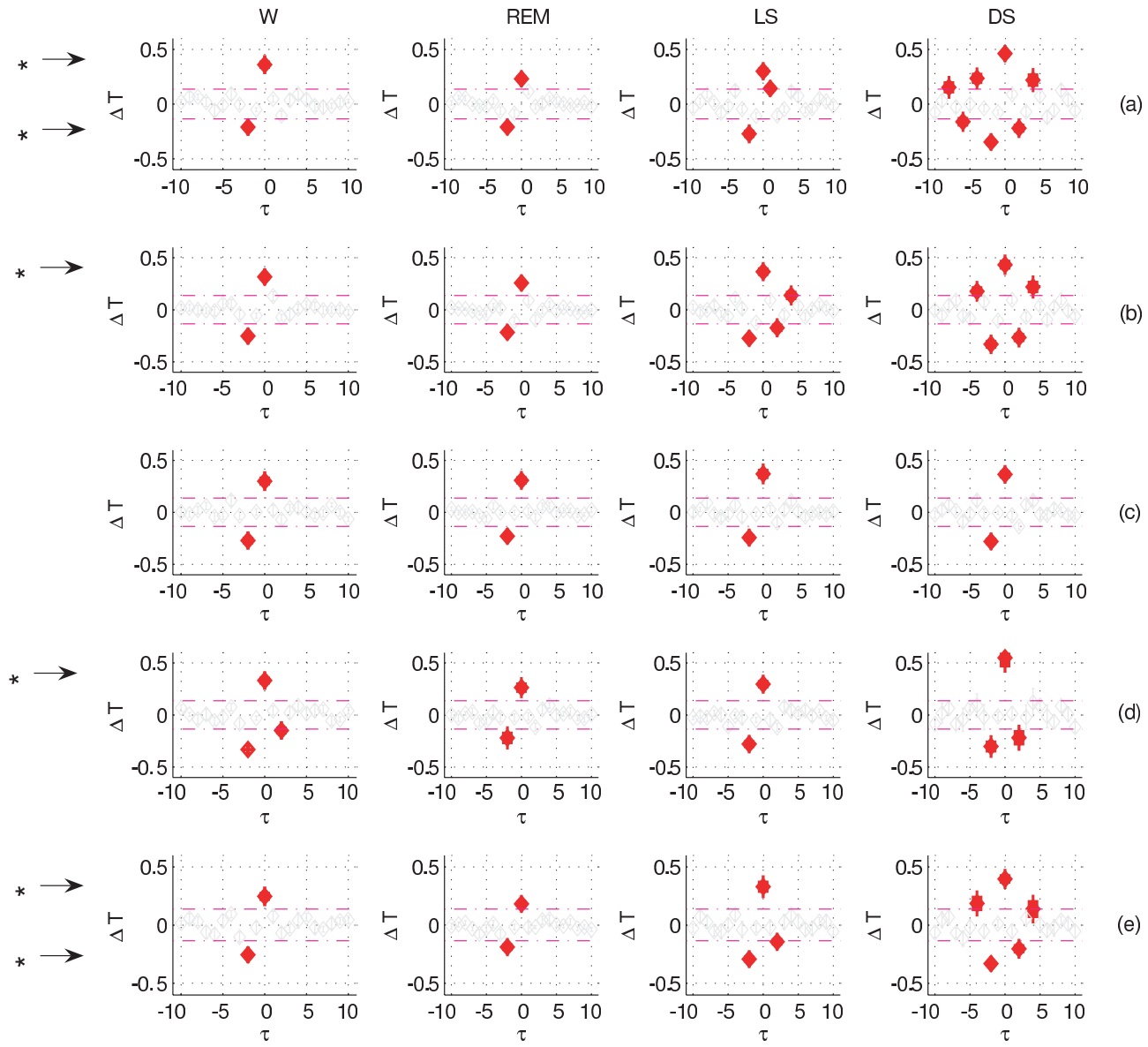

Figure 1. The comparison between the sleep stages (wake = W, REM-sleep = REM, light sleep = LS, deep sleep = DS) and the different patient groups (healthy controls - a, NT DD - b, NT CPAP - c, HT DD - d, HT CPAP - e) clearly shows the short term asymmetry in the coupling during wake and REM characterised by lags $\tau = -2$ and $\tau = 0$. This asymmetry becomes less in light sleep and is lost in deep sleep when periodic breathing leads to a modulation of B_i and S_i. Significant differences in the coupling strength at $\tau = 0$ and $\tau = -2$ between the sleep stages are marked by $\star$ ($p < 0.05$, Kruskal-Wallis test). Differences exist at both lags in the control patients group as well as HT CPAP. In NT DD and HT DD only the lag $\tau = 0$ is significantly different between the sleep stages. This figure is taken from Suhrbier et al. 2010 [8].

Considering the CPAP therapy, we see that there are no different coupling patterns before and after treatment during the wake and the REM state. However, during deep sleep, we see clear differences in the cardiovascular couplings (Fig. 1). These results are confirmed by the parameters of heart rate and blood pressure variability (see Tab. 2), mainly by HF-S (Tab. 2) which reflects the mechanical effects of respiration on blood pressure [11]: The higher the HF-S, the higher the respiratory effort. 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 significant improvements during light sleep in the normotensive group and

Table 2. Mean and standard deviation (mean± std) of high frequency component of B_i and S_i (HF-B, HF-S; $0.15 \leq f \leq 0.4$Hz), low frequency component of B_i and S_i (LF-B, LF-S; $0.04 \leq f \leq 0.15$Hz) and baroreceptor sensitivity (BRS) for healthy controls (C), normotensive (NT) and hypertensive (HT) patients suffering from obstructive sleep apnoea syndrome (OSAS) during night (DD) as well as treatment by means of continuous positive airway pressure (CPAP). Significant differences between sleep stages within the patient groups are marked by $\star$ ($p < 0.05$), between DD and CPAP are marked by † ($p < 0.05$) and between patient groups NT/HT and C respectively are marked by $\diamond$ ($p < 0.05$). For testing, a Kruskal-Wallis test is used.

Sleep stage	Parameter	NT OSAS		HT OSAS		C
		DD	CPAP	DD	CPAP	DD
W	HF-B	20.38 ± 13.28	62.97 ± 146.52	$8.44 \pm 6.36\star$	15.23 ± 23.25	20.75 ± 16.59
	LF-B	72.79 ± 84.72	89.47 ± 167.56	$44.17 \pm 54.03\star$	32.46 ± 40.17	33.43 ± 10.19
	HF-S	$0.21\pm 0.12\star$	0.26 ± 0.27	0.14 ± 0.08	0.21 ± 0.17	0.18 ± 0.11
	LF-S	$0.64\pm 0.40\star$	0.91 ± 1.02	0.93 ± 0.95	0.55 ± 0.38	0.74 ± 0.45
	BRS	11.19 ± 3.56	10.42 ± 3.77	8.87 ± 2.40	9.27 ± 3.32	11.44 ± 2.26
LS	HF-B	46.43 ± 46.78	42.79 ± 66.49	37.1 ± 26.90	20.16 ± 17.89	40.80 ± 43.73
	LF-B	108.95 ± 120.88	75.81 ± 66.14	$142.21 \pm 121.11\dagger$	36.92 ± 28.65	74.67 ± 85.31
	HF-S	$0.6\pm 0.67\diamond\dagger$	0.1 ± 0.11	$0.35 \pm 0.21\dagger$	0.1 ± 0.08	0.24 ± 0.28
	LF-S	1.78 ± 2.58	0.89 ± 1.14	$1.61 \pm 1.22\dagger$	$0.56 \pm 0.53\diamond$	1.32 ± 1.01
	BRS	$9.26\pm 2.66\dagger$	12.64 ± 3.95	9.88 ± 1.96	11.24 ± 3.70	11.49 ± 3.49
DS	HF-B	35.37 ± 35.30	45.99 ± 87.22	33.22 ± 19.04	16.97 ± 14.23	29.91 ± 28.89
	LF-B	42.78 ± 38.04	55.19 ± 81.62	33.09 ± 31.92	51.23 ± 95.74	41.03 ± 33.30
	HF-S	$0.65\pm 0.51\diamond\dagger$	0.12 ± 0.10	$0.77 \pm 0.68\dagger$	0.14 ± 0.16	0.26 ± 0.24
	LF-S	0.64 ± 0.59	0.46 ± 0.42	1.84 ± 3.33	0.59 ± 0.68	0.61 ± 0.40
	BRS	7.68 ± 3.23	11.38 ± 3.83	$6.87 \pm 1.72\dagger$	10.76 ± 3.85	11.02 ± 3.70
REM	HF-B	29.57 ± 44.61	42.30 ± 106.72	33.08 ± 51.98	15.21 ± 13.29	42.15 ± 58.62
	LF-B	60.84 ± 44.32	95.84 ± 192.31	170.48 ± 280.99	62.96 ± 39.73	127.07 ± 159.03
	HF-S	0.24 ± 0.19	$0.17 \pm 0.27\diamond$	0.29 ± 0.22	$0.10 \pm 0.07\diamond$	0.24 ± 0.18
	LF-S	1.17 ± 0.83	$0.76 \pm 0.78\diamond$	2.08 ± 2.85	1.10 ± 0.73	2.20 ± 2.79
	BRS	9.73 ± 3.60	10.85 ± 3.58	9.25 ± 2.74	10.87 ± 3.10	10.34 ± 4.09

during deep sleep in the hypertensive group, which confirms the results of [12] where mean BRS increased only slightly during CPAP application. 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.
Summarizing, the proposed method of the symbolic coupling traces may help to indicate pathological changes in cardiovascular regulation and also effects of continuous positive airway pressure therapy on the cardiovascular system.

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