Cardiovascular Regulation in Different Sleep Stages in the Obstructive Sleep Apnea Syndrome

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Abstract

*In order to show the value of the analysis of heart rate variability (*HRV*), blood pressure variability (*BPV*) and baroreflex sensitivity (*BRS*) for the study of sleep disorders we consider 38 subjects, 18 of which are normotensive (*NT*) and 10 hypertensive (*HT*) patients suffering from obstructive sleep apnea syndrome (*OSAS*), the rest being controls. To detect differences in cardiovascular regulation between the different sleep stages and these age and sex matched groups, linear and nonlinear parameters are used. The therapeutic effect of continuous positive airway pressure (*CPAP*) therapy is investigated by comparing an initial diagnostic measurement with a follow-up after three month of therapy.*

1. Introduction

Sleep is a complex phenomenon whose internal structure is currently described as a sequence of sleep stages. While this description is predominantly based on features of the electroencephalogram (EEG), other systems such as the cardiovascular one are clearly also affected by this structure.

Rapid eye movement sleep (REM) presents a level of sympathetic activity that is very similar in the averages of blood pressure (BP) and heart rate (HR) to the ones found while awake (W). The non-REM sleep on the other hand is a phase of relative autonomic stability, dominated by sympathetic inhibition and an increase in vagal tone. Bradycardia, enhanced respiratory sinus arrhythmia (RSA) and an increased baroreceptor gain are the usual results. The average BP decreases from wakefulness to light sleep (LS) and reaches its minimum in deep sleep (DS).

Epidemiological studies confirm a causal relation between sleep disorders and a number of cardiovascular diseases [1]. An important of such disorders is the OSAS, which means a patient has more than 15 respiratory events per hour, respectively an apnea hypopnea index (AHI) of 15. These closures of the upper airways lasting longer than $10\,\mathrm{s}$ can be either complete, a so called obstructive apnea, or partial, meaning a reduction of airflow of more than 50%, called hypopnea. The rising sympathetic activity, assumed to be caused by the rising level of carbon dioxide in the blood, is one of the main factors that leads to a rise in BP of up to $250/110\,\mathrm{mmHg}$ at the moment the obstruction is cleared [2].

A powerful tool for the assessment of such changes in autonomic control and cardiovascular state has been developed in the last 20 years with the analysis of HRV and BPV [3,4]. In this article the diagnostic relevance in parameters of HRV and BPV for detecting and evaluating pathological changes in cardiovascular regulation should be exemplarily demonstrated. Therefore differences in this regulation between the sleep stages as well as those resulting from OSAS shall be investigated. In addition to a comparison to sleep healthy controls, the effects of CPAP are considered.

2. Methods

2.1. Data

This study investigates cardiovascular regulation in different sleep stages on data obtained through polysomnog-

Table 1. Overview of the subjects in the control group (C) as well as normotensive (NT) and hypertensive (HT) obstructive sleep apnea syndrome (OSAS) patients in regard to blood pressure (BP), age, body mass index (BMI) and apnea hypopnea index (AHI)

Group	N	BP (mmHg)	Age (years)	BMI (kg/m^2)	AHI
C	10	$123 \pm 11/84 \pm 5$	44.8 ± 6.7	25.3 ± 2.7	1.2 ± 1.6
NT	18	$120 \pm 19/81 \pm 7$	44.6 ± 7.6	30.2 ± 2.9	42.5 ± 23.9
HT	10	$142 \pm 4/93 \pm 8$	44.1 ± 8.1	34.1 ± 4.9	71.7 ± 32.7

raphy of 38 subjects, 28 of which suffered from OSAS. These subjects where measured thrice: One diagnostic night (labeled DD) followed by a consecutive treatment night using CPAP and a follow-up night (labeled CPAP) after three month of treatment.

In order to assess the relationship to elevated BP, we seperatly consider the 18 normotensive (NT) and 10 hypertensive (HT) patients. Hypertension was defined by an office systolic BP (SBP) higher than $140\,\mathrm{mmHg}$ or diastolic BP (DBP) higher than $90\,\mathrm{mmHg}$.

A group of 10 normotensive and sleep healthy persons were examined in a polysomnographic diagnostic night as controls (C). All groups were age and sex matched (all subjects were male) and a comparison is provided in table 1. Excluding criteria were comorbid illnesses such as diabetes, renal failure or heart rhythm disturbances. This study was approved by the local ethics committee and the informed consent of all subjects was obtained.

Standard polysomnographs were recorded with the addition of continuous BP measured using a finger cuff (Portapres device model 2, BMI-TNO, Amsterdam, The Netherlands). The recordings were classified according to Rechtschaffen and Kales [5] to derive the sleep stage for each 30s epoch and the respiratory events, i.e. apneas and hypopneas. In this study, sleep stages S1, S2 and S3, S4 were combined as LS and DS respectively.

2.2. Measures

To investigate the cardiovascular regulation non-invasively we use statistical time-domain and frequency-domain measures as proposed by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [3]. To allow statistical measures of variability that require stationary conditions in the underlying process, only the first 5 minutes of the largest undisturbed period of each sleep stage is considered for each subject. In some cases disturbances, such as repetitive episodes of apneas or hypopneas or artifacts due to calibration or measurement error, are so frequent that no 5 minute epoch is available for analysis. The resulting variable number of epochs is presented in Table 2.

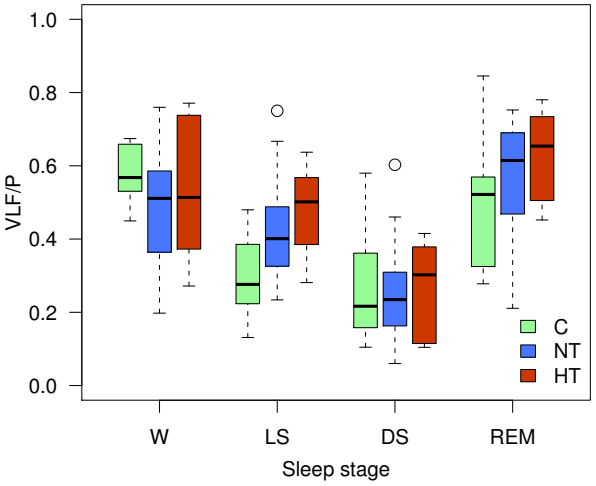
The time domain parameters of HRV, BPV as well as BRS are used to characterize the autonomous regulation in different sleep stages and quantify the impacts of OSAS and associated hypertension on the vegetative control. Parameters in the frequency domain of HRV can be used to distinguish sources of influence. While the power in the frequency band between $0.15\,\mathrm{Hz}$ and $0.4\,\mathrm{Hz}$ (HF) is generally accepted as a reflection of the vagally induced respiratory oscillations in HR, there is controversial discussion about the power in the range of $0.04\,\mathrm{Hz}$ to $0.15\,\mathrm{Hz}$ (LF) as a marker of sympathetic activity. This is due to the rather unknown vagal influence on this spectral band. Oscillations in the power in frequencies $\leq 0.04\,\mathrm{Hz}$ (VLF) are considered to be the result of neuroendocrine regulation such as the Renin-Angiotensin system [6]. Applied to the BPV of the SBP and DBP, HF is thought to be generated by the mechanical influence of the respiratory movement on the intra-thoracic pressure whereas LF quantifies the sympathetic activity through the peripheral resistance of the vessels [7].

The BRS, which has proven to be an important marker for BP-HRV interaction, is defined as the reflectory change of beat-to-beat intervals (BBIs) related to increasing or decreasing SBP. The sequence method provides a simple tool for the estimation of this parameter. It works by scanning the SBP time series, identifying sequences of monotonic increases/decreases of length 3 with synchronous counterparts in BBI. The mean of the slopes of the regression line of BBI against BP for the SBP sequences is taken as an estimate of BRS [8].

Table 2. Number of selected data sets for all groups (control (C), normotensive patients (NT) and hypertensive patients (HT)) and sleep stages (nocturnal epochs of awake stage (W), light sleep (LS), deep sleep (DS) and rapid eye movement sleep (REM))

Group	Night	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

Figure 1. Normalized power of the very low power spectral band (0.0033–0.04 Hz) for control subjects (C) as well als normotensive (NT) and hypertensive (NT) patients in all sleep stages during the diagnostic night. Kruskal-Wallis test for differences between the sleep stages is significant for each group (C and NT: $p < 0.001$, HT: $p < 0.01$).



The field of non-linear dynamics provides tools that help to describe those properties of HRV and BPV that cannot be captured using linear parameters [4, 9]. Non-linear features based on symbolic dynamics, such as the word distribution Shanon entropy (FWSHANNON), have been proven to be very sucessfull in describing complex behaviour and are applied as described in [10].

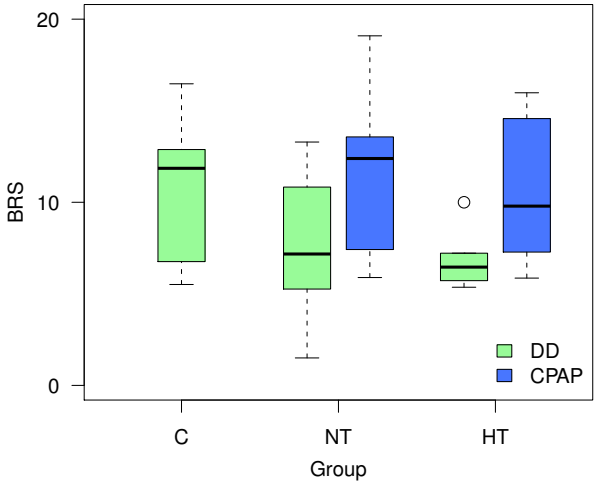
2.3. Statistical analysis

Each parameter is seperately compared using a Kruskal-Wallis test for each group and sleep stage to detect sleep-stage-dependent changes in cardiovascular short term regulation. A Mann-Whitney test is applied to significant parameters to reveal the amount of contribution of the different sleep-stages. The influence of CPAP on parameters of HRV and BPV is evaluated by means of a Mann-Whitney test. The parameters are compared between the DD and CPAP nights for each sleep stage in groups NT and HT. All statistical data processing is performed using SPSS version 18.

3. Results

Our study shows that several HRV and BPV parameters adequatly reflect complex sleep dynamics, demonstrating appreciable differences between sleep stages. Due to limits on available space and for reasons of comprehensibility only a limited set of the most significant parameters are presented here. Further results are available in [11].

Figure 2. Baroreceptor sensitivity (BRS) during deep sleep (DS) for control subjects (C) as well as obstructive sleep apnea syndrome (OSAS) patients furing the diagnostiv night and after three month of continuous positive airway pressure (CPAP) for normotensive (NT) and hypertensive (HT) OSAS patients. Mann-Whitney tests show a significant improvement in BRS (NT: 7.67 ± 32 vs. 11.4 ± 3.8 ms/mmHg, $p = 0.007$; HT: 6.87 ± 1.7 vs. 10.7 ± 3.8 ms/mmHg, $p = 0.02$)



Significant differences between the sleep stanges in all three goups are identifiable in the HRV parameter of VLF normalized to the full spectral power (VLF/P) in BBI (C and NT: $p < 0.001$, HT $p < 0.01$, cf. Figure 1). Mann-Whitney tests allow a more detailed comparison and reveal significantly changed values between: W and LS (C: $p < 0.001$), W and DS (C: $p < 0.01$, NT: $p < 0.01$, HT: $p < 0.05$), LS and DS (NT: $p < 0.01$, HT: $p < 0.05$), LS and REM (C: $p < 0.01$, NT: $p < 0.01$) as well as DS and REM (C: $p < 0.05$, NT: $p < 0.01$), HT: $p < 0.01$).

For BPV data, FWSHANNON of the SBP beat-to-beat time series successfully demonstrates regulatory changes between the sleep stages. The Kruskal-Wallis test shows significant differences for all groups (C and HT: $p < 0.05$, NT: $p < 0.01$). The detailed analysis using Mann-Whitney tests produces significant differences between: W and LS (C and HT: $p < 0.05$, NT: $p < 0.01$), W and DS (C, NT and HT: $p < 0.01$), W and REM (NT and HT: $p < 0.05$), LS and REM (NT: $p < 0.05$), and DS and REM (NT: $p < 0.0001$).

Evaluating the effects of CPAP on OSAS patients, BRS shows significant increases during non-REM sleep stages. Mann-Whitney tests reveal this improvement in LS (NT: 9.26 ± 2.6 vs. 12.6 ± 3.9 ms/mmHg, $p = 0.007$) and DS (NT: 7.67 ± 3.2 vs. 11.4 ± 3.8 ms/mmHg, $p = 0.007$; HT: 6.87 ± 1.7 vs. 10.7 ± 3.8 ms/mmHg, $p = 0.02$; cf. Figure 2).

4. Discussion and conclusions

The presented results demonstrate the importance of HRV and BPV analysis in the investigation of the autonomous nervous system. The difference in regulation in the different sleep stages are clearly shown. Additionally a positive effect of the three month CPAP therapy can be quantified using BRS.

The most pronounced changes in regulation during different sleep stages can be identified between DS and REM (cf. Figure 1). The substantial decrease in VLF/P of HRV apparent during non-REM sleep, particularly DS, may be presumed to arise through the depressed metabolic activity [6, 12]. This agrees with results of a study by Schumann et al. [13], which showed similar effects by means of detrended fluctuation analysis in that the long term correlations decrease in non-REM sleep in healthy subjects.

Both groups of OSAS patients (NT and HT) show a clear reduction of this effect where no differences between W and LS are visible. These changes are attributed to effects due to OSAS as they disappear in the follow-up measurement after CPAP treatment. A previous study by Hedner et al. using biomarkers [14] found reduced sympathetic activity after long-term CPAP treatment, which the results of our study confirm.

In healthy persons, the rising dominance of the parasympathicus, from W and REM to LS and finally DS, is accompanied by a lower FWSHANNON. This indication of more deterministic BP fluctuations is caused by an increase of compliance in the whole arterial system [15]. An overactivation of the sympathetic drive in OSAS patients leads to decreased FWSHANNON values for all sleep stages.

The increase of BRS, as a measure of the coupling between HR and BP, in all patients after three month of CPAP treatment towards those values found in controls, indicates a regression of a previous regulatory dysfunction (cf. Figure 2). This finding confirms previous findings of CPAP-based improvement of BRS [16].

The small number of OSAS patients and controls as well as the non-ubiquity of undisturbed epochs for each sleep phase are a limitation of this study. No repeated measure tests could be applied as a result. To confirm our findings, prospective studies with larger patient and control groups are needed.

Acknowledgements

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