Biomed Tech 2011; 56:207–213 © 2011 by Walter de Gruyter • Berlin • Boston. DOI 10.1515/BMT.2011.018

# Cardiovascular regulation in different sleep stages in the obstructive sleep apnea syndrome

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## Abstract

Heart rate and blood pressure variability analysis as well as baroreflex sensitivity have been proven to be powerful tools for the assessment of autonomic control in clinical practice. Their ability to detect systematic changes caused by different states, diseases and treatments shall be shown for sleep disorders. Therefore, we consider 18 normotensive and 10 hypertensive patients suffering from obstructive sleep apnea syndrome (OSAS) before and after a three-month continuous positive airway pressure (CPAP) therapy. Additionally, an age and sex matched control group of 10 healthy subjects is examined. Linear and nonlinear parameters of heart rate and blood pressure fluctuation as well as the baroreflex sensitivity are used to answer the question whether there are differences in cardiovascular regulation between the different sleep stages and groups. Moreover, the therapeutic effect of CPAP therapy in OSAS patients shall be investigated. Kruskal-Wallis tests between the sleep stages for each group show significant differences in the very low spectral component of heart rate (VLF/P: 0.0033–0.04 Hz, $p < 0.01$) which indicates differences in metabolic activity during the night. Furthermore, the decrease of Shannon entropy of word distribution as a parameter of systolic blood pressure during non-REM sleep reflects the local dominance of the vagal system ($p < 0.05$). The increased sympathetic activation of the patients leads to clear differences of cardiovascular regulation in different sleep stages between controls and patients. We found a significant reduction of baroreflex sensitivity in slow wave sleep in the OSAS patients (Mann-Whitney test, $p < 0.05$) compared to controls, which disappeared after three months of CPAP therapy. Hence, our results demonstrate the ability of cardiovascular analyzes to separate between healthy and pathological regulation as well as between different severities of OSAS in this retrospective study.

**Keywords:** baroreflex sensitivity; blood pressure variability; heart rate variability; obstructive sleep apnea syndrome.

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## Introduction

During the last 20 years, the analysis of heart rate and blood pressure variability (HRV and BPV, respectively) has become a powerful tool for the assessment of autonomic control and cardiovascular state in clinical practice. Different measures based on these biosignals have proven to be independent predictors of different cardiovascular diseases and pathological events, e.g., sudden cardiac death after acute myocardial infarction, chronic heart failure or dilated cardiomyopathy [5, 11, 13, 16–18, 25, 26, 38]. There are simple statistical measures as well as sophisticated parameters of time series analysis taken from engineering and theoretical physics [9, 31, 40]. However, their interpretation is difficult due to the complexity of HRV and BPV caused by non-linear interactions and numbers of simultaneously working control loops with different time scales and with different time delays [19].

An example of the clinical relevance of HRV and BPV is their use in sleep medicine [24, 29]. Sleep is a complex phenomenon which is characterized by a sequence of different sleep stages. Electroencephalographic recordings are used for their differentiation. The sleep stages modulate the activity of the autonomous nervous system that leads in turn to changes in the pattern of cardiovascular oscillations [23, 34, 36]. From the cardiovascular perspective, non-REM sleep is a phase of relative autonomic stability. These stages are dominated by sympathetic inhibition and an increase in vagal tone. It usually leads to bradycardia, enhanced respiratory sinus arrhythmia, and an increased baroreceptor gain. The blood pressure (BP) decreases from wakefulness to light sleep and reaches its minimum in deep sleep. During rapid eye movement (REM) sleep, there is increased sympathetic activity with averages of blood pressure (BP) and heart rate (HR) similar to their levels during wakefulness. Additionally, respiratory irregularities during REM contribute to an increased complexity of HRV and BPV [23, 36].

Due to the link between the sleep stages and cardiovascular regulation, disturbances of sleep also affect the auto-

nomic nervous system, systemic hemodynamics, cardiac function, and endothelial function. Epidemiological studies confirm this causal relation between sleep disorders, e.g., sleep deprivation, shift work, and sleep disordered breathing, and a number of diseases, e.g., hypertension, atherosclerosis, stroke, heart failure, cardiac arrhythmias, and sudden death [6, 42]. One important sleep disorder is the obstructive sleep apnea syndrome (OSAS), where more than 15 apnea and hypopnea events appear per hour of sleep. Obstructive apneas are closures of the upper airway lasting more than 10 s. The partial occlusion is called hypopnea and is characterized by a reduction of airflow of at least 50% over a period longer than 10 s. The sympathetic activity and BP during sleep is determined by the responses to these pathological respiratory disorders in patients suffering from OSAS. The level of carbon dioxide in the blood during apnea is assumed to be a key factor causing increased sympathetic activation. The sympathetic activity rises gradually during the apnea and reaches its maximum at the end of this episode. Once the airway obstruction is cleared, the combination of increasing cardiac output and vasoconstricting effects of the high sympathetic activity leads to a rise in BP reaching up to 250/110 mm Hg [4, 24].

Studies of cardiovascular variability in patients suffering from OSAS have indeed shown distinctly abnormal patterns of HRV and BPV during sleep [8, 28, 35]. Therefore, there is diagnostic relevance in parameters of HRV and BPV for detecting and evaluating pathological changes in cardiovascular regulation caused by this disease. In this article, this ability of the cardiovascular variability parameters should be exemplarily demonstrated. For this reason, differences of the cardiovascular regulation in different sleep stages are investigated. Additionally, changes in the regulation caused by the sleep apnea syndrome are considered, comparing a group of healthy subjects and patients suffering from this disease. Moreover, the effect of continuous positive airway pressure therapy (CPAP) on these differences is discussed.

## Materials and methods

### Data

For the characterization of cardiovascular regulation in different sleep stages, we consider 18 normotensive (NT) and 10 hypertensive patients (HT) suffering from OSAS before and after three months of CPAP therapy. The hypertensive patients were defined by an office systolic blood pressure higher than 140 mm Hg or diastolic blood pressure higher than 90 mm Hg. The mean values were $142 \pm 4/93 \pm 8$ mm Hg in HT and $120 \pm 10/81 \pm 7$ mm Hg in NT.

Additionally, a control group of 10 healthy controls (C) is examined. The groups HT (age: $44.1 \pm 8.1$ years, all male), NT (age: $44.6 \pm 7.6$ years, all male), and C (age: $44.8 \pm 6.7$ years, all male) are age and sex matched. The group means of the body mass index are $25.3 \pm 2.7$ kg/m$^2$ (C), $30.2 \pm 2.9$ kg/m$^2$ (NT) and $34.1 \pm 4.9$ kg/m$^2$ (HT). In C, the mean office blood pressure was $123 \pm 11/84 \pm 5$ mm Hg.

The apnea-hypopnea indices in the groups are $1.2 \pm 1.6$ (C), $42.5 \pm 23.9$ (NT) and $71.7 \pm 32.7$ (HT). Excluding criteria were comorbidities such as diabetes, renal failure or rhythm disturbances. For each patient, polysomnographical measurements of a diagnostic night and a night of treatment by means of CPAP were performed, where these measurements were separated by a three-monthly CPAP therapy. The polysomnographic recordings include electroencephalogram, electrooculogram, electromyogram, respiratory airflow, electrocardiogram (sampling rate of 1000 Hz), and continuous BP (via finger cuff of Portapres device model 2, BMI-TNO, Amsterdam, The Netherlands; sampling rate of 200 Hz). This study was approved by the local ethics committee and the informed consent of all subjects was obtained.

From the electrocardiogram, the intervals between successive heartbeats – beat-to-beat intervals (BBIs) – are calculated using appropriate algorithms [37]. The BBI represent the inverse HR. Artifacts caused by, e.g., premature beats are exchanged in BBI by means of interpolation using an adaptive filter [40]. Additionally, the maximum BP value in each BBI is extracted from the continuous BP signal, which leads to the time series of systolic blood pressure (SBP) on a beat-to-beat basis. The same procedure is done by using minimum BP values to extract the beat-to-beat diastolic blood pressure (DBP). The variability of BBI, SBP, and DBP is used to characterize the short-term regulation of the cardiovascular system.

In order to analyze this regulation in relation to different sleep stages, electroencephalogram, electrooculogram, and electromyogram are used to classify successive 30 s epochs of sleep [32]. We consider light sleep (LS: containing sleep stages S1 and S2), deep sleep (DS: containing sleep stages S3 and S4), rapid eye movement (REM), and nocturnal epochs of awake stage (W). Additionally, respiratory flow (oro-nasal thermistor), respiratory effort (thoracic and abdominal plethysmographic belt), and saturation of blood oxygen (plethysmogram) are used to define the events of apnea and hypopnea. The frequency of these respiratory disturbances ($>15$ events/h) characterizes the HT and NT as OSAS patients.

For all sleep stages, W, LS, DS, and REM, the variability of BBI, SBP, and DBP as well as the baroreflex sensitivity (BRS) are quantified. Because the statistical measures of variability require stationary conditions in the underlying process, only the first 5 min of the largest undisturbed period of each sleep stage in each subject is considered where stationarity is assumed. Disturbances include the repetitive episodes of apneas and/or hypopneas as well as artifacts of calibrations and measurement errors. The first 5 min of sufficient quality are selected automatically for analysis. In some cases, no undisturbed epochs of 5 min are available, so the size of the groups varies (see Table 1). Examples of BBI and SBP of selected sleep periods are shown in Figure 1.

### Measures

The parameters of HRV and BPV as well as BRS are commonly accepted tools for non-invasive investigation of cardiovascular regulation. In this study, these measures are used

**Table 1** Number of selected data sets for the investigated groups (C, healthy controls; NT, normotensive patients; HT, hypertensive patients; DD, differential diagnosis night; CPAP, night with continuous positive airway pressure therapy after three months of this treatment) and for different sleep stages (W, awake stage; LS, light sleep; DS, deep sleep; REM, rapid eye movement).

| 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 |

to characterize the autonomous regulation during the different sleep stages and to quantify the impact of OSAS as well as associated hypertension on the vegetative control during sleep. We use the statistical time-domain measures and frequency-domain parameters proposed by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [9].

The frequency domain parameter HF reflects mainly the vagally induced respiratory oscillations in HR. The LF component as a marker of sympathetic activity is controversially discussed because the vagal influence on this spectral band is rather unknown. Oscillations of the VLF band are considered to be the result of neuroendocrine regulation, e.g., Renin-Angiotensin system [1]. To account for non-linear properties of HRV and BPV, complexity measures from the field of non-linear dynamics are considered [15, 21, 30, 39, 40]. One prominent example is the Shannon entropy (Eq. 1) which is defined by

$$SHANNON(p_1,...,p_n) = -\sum_{i=1}^{n} p_i \ln p_i \tag{1}$$

where $p_1>0,...,\ p_n>0$ are the normalized histogram of the HR or BP values.

To describe complex behavior, features based on symbolic dynamics features have been proven to be very successful. One of them is the word distribution Shannon entropy or FWSHANNON (Eq. 3). For calculation of this parameter, the measurement $x$ is encoded by

$$s_n = \begin{cases} 0: & \mu & < x_n \le & (1+a)\mu \\ 1: & (1+a)\mu & < x_n < & \infty \\ 2: & (1+a)\mu & < x_n \le & \mu \\ 3: & 0 & < x_n \le & (1-a)\mu \end{cases} \tag{2}$$

where $\mu$ denotes the adaptive mean of $x$, $a$ fixes the segmentation of its domain, and $n$ is the index of the values. In different studies $a=0.05$ is chosen not only for HR but also BP signal [40]. For appropriate statistical estimation of the word distribution, words of the four symbol alphabet 0,1,2,3 and length 3 are analyzed. The Shannon entropy of that distribution is

$$FWSHANNON = -\sum_{p(w_i)>0} p(w_i)\log p(w_i) \tag{3}$$

where $w_i$ is the i-th word of the 64 ($4^3$) possible ones. FWSHANNON takes the regular behavior beyond a noise level into account. If there are regular or frequent changes

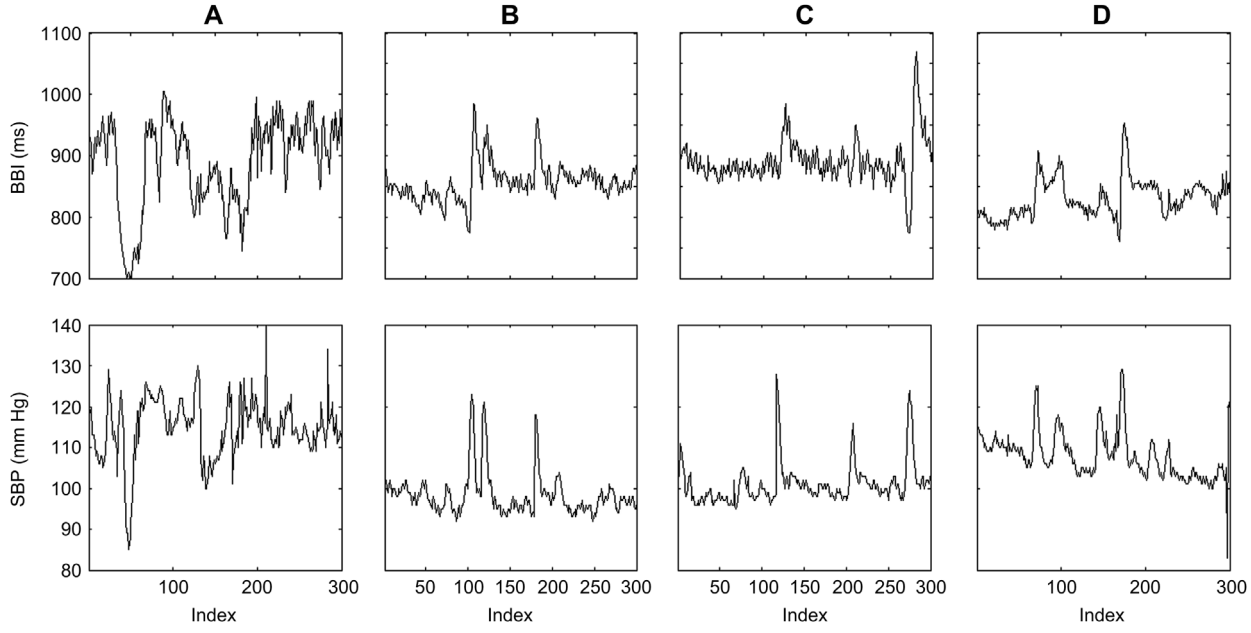


**Figure 1** Extracted time series of beat-to-beat interval (BBI) and systolic blood pressure (SBP) for a healthy subject during different sleep stages: wake (column A); light sleep (column B); deep sleep (column C); and REM sleep (column D).

to extreme values of the HR or BP, the value of FWSHANNON increases. Otherwise, a low value characterizes a laminar behavior in the limits of the noise level.

These parameters can also be used for the description of fluctuations in systolic and diastolic blood pressure after adaptation to the physiological settings (via a threshold) in the definitions of complexity parameters. For instance, the HF component of BPV characterizes the mechanical influence of the respiratory movement on the intra-thoracic pressure and LF quantifies the sympathetic activity which regulates the peripheral resistance of the vessels [27]. Therefore, BPV is an additional tool characterizing the cardiovascular control. Generally, a sustained period of depressed HRV as well as an increased BPV indicates pathological changes of the cardiovascular short-term regulation [9, 40].

The spontaneous BRS has proven to be an important marker for BP–HR interactions. The BRS is defined as the reflectory change of BBI related to increasing or decreasing values in SBP. A simple approach to its estimation is the sequence method. This time-domain method scans the beat-to-beat systolic pressure series to identify sequences of length 3 with monotonic BP increases (or decreases) and synchronous increases (or decreases) of BBI. The mean slope of the regression line between ramps of BBI and SBP values within the sequence is taken as an estimate of BRS [21, 22].

### Statistical analysis

In order to find sleep-stage-dependent cardiovascular short-term regulation, a Kruskal-Wallis test compares each parameter of HRV and BPV separately during all sleep stages for each group. For significant parameters, Mann-Whitney tests were applied to reveal which sleep stages contribute to the differences found. In addition to the assessment of sleep stage influence on the cardiovascular short-term regulation, the effect of CPAP therapy on parameters of HRV and BPV is evaluated by means of a Mann-Whitney test. In these tests, the parameters before and after three months of therapy are compared for each sleep stage in NT and HT. All statistical data processing is done with SPSS version 18.

## Results

One of the main findings of this study is that several HRV and BPV parameters adequately reflect complex sleep dynamics and demonstrate differences between sleep stages. For comprehensibility, only the most significant parameters are presented here. Most of the other significant parameters show similar behavior, because they are correlated to the ones present here [9].

In the set of HRV parameters the most prominent measure is the normalized spectral power in very low frequency (VLF/P) which reflects the power of the frequency band (0.0033–0.04 Hz) (cf. Figure 2) in BBI. The Kruskal-Wallis test shows significant differences between the sleep stages for all three groups (C and NT groups $p<0.001$, HT group $p<0.01$, cf. Figure 2). A more detailed analysis by means of Mann-Whitney tests reveals significantly changed values of VLF/P between: W and LS (C: $p<0.001$), W and DS (C: $p<0.01$, NT: $p<0.01$, and HT: $p<0.05$), LS and DS (NT: $p<0.01$, HT: $p<0.05$), LS and REM (C: $p<0.01$, and NT: $p<0.01$), DS and REM (C: $p<0.05$, NT: $p<0.01$, and HT: $p<0.01$). There is, on the one hand, an increase of VLF/P in OSAS patients (NT and HT) during LS and REM while on the other hand VLF/P is decreased during W in comparison to healthy subjects (see Figure 2).

FWSHANNON is the most representative SBP variability feature. The Kruskal-Wallis test for differences between the sleep stages shows significant differences for each group (C and HT: $p<0.05$, and NT: $p<0.001$, cf. Figure 3), where the Mann-Whitney tests yield significant changes between: W and LS (C and HT: $p<0.05$, and NT: $p<0.001$), W and DS (C, HT, and NT: $p<0.01$), W and REM (NT and HT: $p<0.05$), LS and REM (NT: $p<0.05$), DS and REM (NT: $p<0.0001$). During all sleep stages, FWSHANNON is decreased in both patient groups (HT and NT) in comparison to healthy subjects (see Figure 3).

The changes of DBP variability in different sleep stages are demonstrated by the Shannon entropy. The Kruskal-Wallis test is significant for the control group ($p<0.05$; cf. Figure 4). Although this test shows overall sleep stages differences in one group only, the applied Mann-Whitney tests indicate significant changes between: W and LS (HT: $p<0.05$), W and DS (C: $p<0.05$), W and REM (HT: $p<0.05$), LS and DS (C and NT: $p<0.05$), DS and REM (C: $p<0.01$). Shannon entropy is increased for patients suffering from OSAS during LS and DS in comparison to the controls, which is related to higher variations in DBP. These differences are more pronounced for patients of the HT group (see Figure 4).

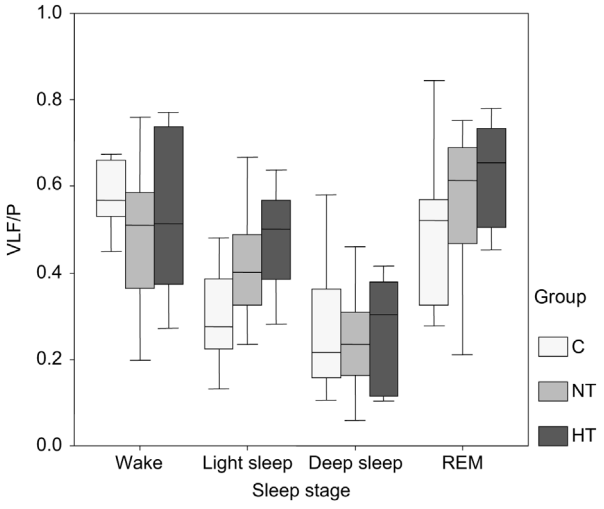


**Figure 2** Heart rate variability: normalized very low frequency power (0.0033–0.04 Hz) of heart rate (VLF/P) for control group (C), normotensive (NT) and hypertensive (HT) obstructive sleep apnea patients in different sleep stages during the diagnostic examination night. Kruskal-Wallis test for differences between the sleep stages is significant for each group (C and NT: $p<0.001$, HT: $p<0.01$). REM, rapid eye movement sleep.

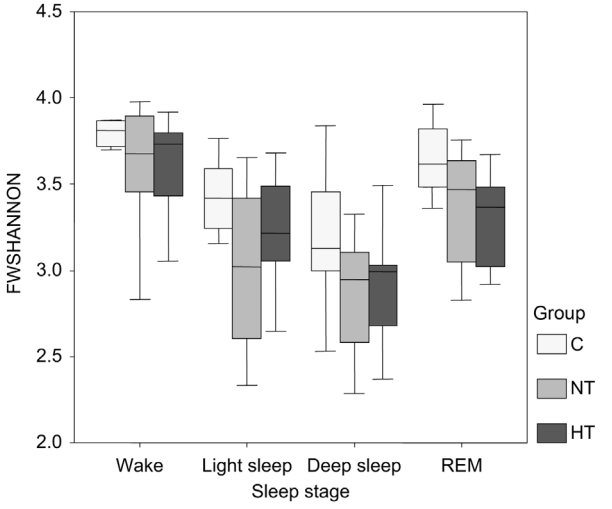


**Figure 3** Systolic blood pressure: Shannon entropy of word distribution (FWSHANNON) for control group (C), normotensive (NT) and hypertensive (HT) obstructive sleep apnea patients in different sleep stages of the diagnostic night. The Kruskal-Wallis test between sleep stages is significant for all groups (C and HT: $p<0.05$, and NT: $p<0.001$). REM, rapid eye movement sleep.

A comparison of BRS in the different sleep stages shows that patients with OSAS have decreased values especially during DS (see Figure 5). The HT group has a lower BRS during W and non-REM sleep (LS and DS). Significant differences between C and OSAS patients (HT and NT) are especially pronounced during DS (Mann-Whitney test: C vs. NT $p<0.05$ and C vs. HT $p<0.01$). In the intra-group comparisons, no group shows significance in the Kruskal-Wallis test for inter-sleep-stages differences.

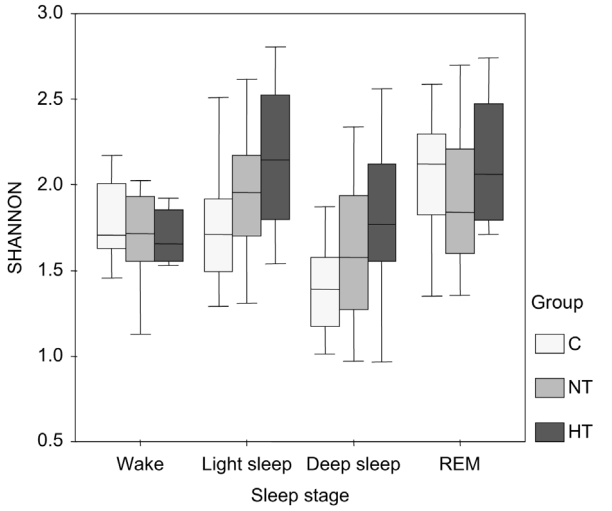


**Figure 4** Diastolic blood pressure: Shannon entropy (SHANNON) of diastolic blood pressure for the control group (C), normotensive (NT) and hypertensive (HT) sleep apnea patients in different sleep stages of the diagnostic night. Kruskal-Wallis test between sleep stages is significant only for group C ($p<0.05$). REM, rapid eye movement sleep.

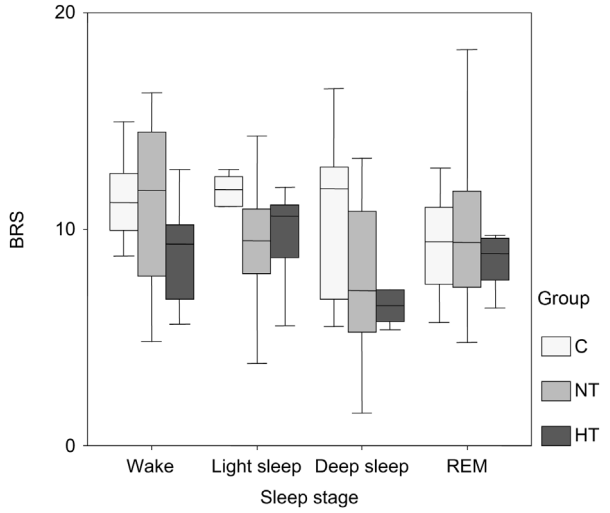


**Figure 5** Baroreflex sensitivity (BRS) in different sleep stages for the control group (C) as well as normotensive (NT) and hypertensive (HT) patients suffering from obstructive sleep apnea syndrome during the diagnostic night. Kruskal-Wallis test between sleep stages was not significant for all three groups. Mann-Whitney test shows significant differences between control group C and both patient groups (NT $p=0.016$ and HT $p=0.004$) during deep sleep (DS). REM, rapid eye movement sleep.

After three months of CPAP therapy, however, there is an increase in BRS in all patients. During REM and W episodes these changes are relatively small but during non-REM sleep (LS and DS) the effect is large. Mann-Whitney tests show a significant improvement in BRS during LS (NT: $9.26\pm2.6$ vs. $12.6\pm3.9$ ms/mm Hg, $p=0.007$) and DS (NT: $7.67\pm3.2$

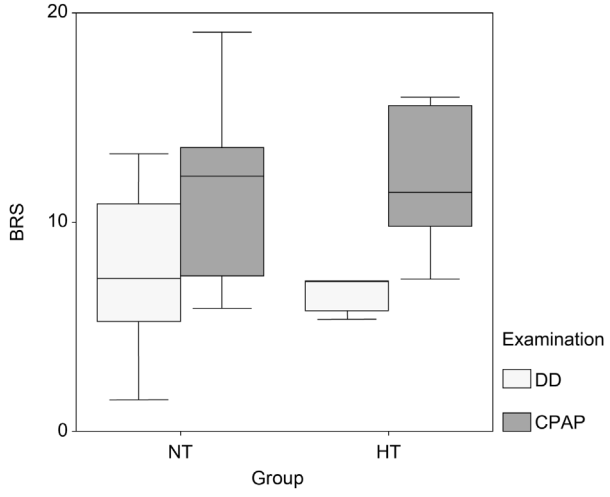


**Figure 6** Baroreflex sensitivity (BRS) during deep sleep for normotensive (NT) and hypertensive (HT) patient groups estimated at the diagnostic examination night (DD) and after three months of continuous positive airway pressure therapy (CPAP). Mann-Whitney tests show a significant improvement in BRS (NT: $7.67\pm3.2$ vs. $11.4\pm3.8$ ms/mm Hg, $p=0.007$; HT: $6.87\pm1.7$ vs. $10.7\pm3.8$ ms/mm Hg, $p=0.02$).

vs. 11.4±3.8 ms/mm Hg, p=0.007; HT: 6.87±1.7 vs. 10.7±3.8 ms/mm Hg, p=0.02; cf. Figure 6).

## Discussion

Our results demonstrate the importance of HRV and BPV analysis in the investigation of the autonomous nervous system. In this study, clearly significant differences of the cardiovascular regulation during different sleep stages are shown. Moreover, a separation of healthy and pathological regulation caused by obstructive sleep apnea syndrome is possible. Additionally, we are able to quantify the positive effect of CPAP therapy through increased baroreflex sensitivity.

Considering sleep stages relative to the cardiovascular regulation, the most pronounced differences are found between DS and REM (see Figure 2). VLF/P of HRV decreases substantially during non-REM, especially in DS, probably due to the depressed metabolic activity [1, 3]. Schumann et al. [33] found similar behavior in long-term correlations by means of detrended fluctuation analysis which are higher during W and REM stages and decreasing during non-REM sleep in healthy subjects.

This effect is much less expressed in the OSAS patients (NT and HT) where VLF/P values do not differ in W and LS. These differences may be considered to be OSAS related because the parameter values are normalized and do not differ significantly from the control group after three months of CPAP therapy. This confirms the results of Hedner et al. [10] who showed that long-term CPAP treatment reduced biochemical markers of sympathetic activity.

Information about the short-term regulation of the cardiovascular system is provided by the analysis of the BPV parameters. The slopes of the shown non-linear parameters, FWSHANNON of SBP and SHANNON of DBP, both arise from the change of the sympatho-vagal activity and their influence to the cardiovascular tissues. In healthy persons, the reduction in these parameters indicates more deterministic BP fluctuations from W and REM to LS and DS (see Figures 3 and 4). Both entropies are minimal in DS which is caused by rising dominance of the parasympathicus leading to more elastic blood vessels. This decreases the peripheral resistance of the smallest arteries and arterioles as well as increases the compliance of the large arteries [41]. On one hand, an increased vagal tone leads to an increased compliance and thus, via the Windkessel function, to lowered random DBP fluctuations (SHANNON decreases). On the other hand, the reduced peripheral resistance causes a more laminar behavior in the SBP variations (FWSHANNON decreases).

In OSAS patients, the decrease of FWSHANNON in SBP for all sleep stages is caused by the over-activation of the sympathetic drive (see Figure 3). The reduced compliance leads to a decreased buffering of HR fluctuations and thus to increased systolic BP variations. Moreover, this effect is enhanced by the increase in peripheral resistance. Furthermore, the so-called Mayer waves in HR may be an additional contributing factor that arises from slow oscillations of the sympathetic vasomotor tone [12].

The Shannon entropy of DBP in OSAS patients is clearly increased during non-REM sleep (LS and DS) in comparison to the healthy controls (see Figure 4). That means the fluctuations of DBP are higher in subjects suffering from OSAS during non-REM sleep. Thus, the decreased buffer function of the large arteries plays the major role by enhancing the transmission of DBP fluctuations of the cardiac output. This difference between healthy subjects and OSAS patients is most explicitly visible during non-REM sleep because the healthy regulation is in these cases dominated by the vagal system.

The analysis of the BRS as a measure of the coupling between HR and BP shows no significant changes related to sleep stages (see Figure 5). A reason could be the short time interval of about 5 min which may lead to less reliable values. A comparison of healthy subjects and OSAS patients indicates a decrease of BRS during non-REM sleep. Obviously, the pathological decrease of the vagal activity during these sleep stages could explain the difference [22]. The three-month CPAP therapy leads to a regression of this dysfunction (see Figure 6) and confirms previous findings of CPAP-based improvement of BRS [2, 14, 20]. All patients showed an increased baroreflex gain, with the most pronounced changes found during LS and DS. After three months of therapy, BRS values of patients with OSAS did not differ from values of the C group.

Limitations of our exploratory study are a small number of OSAS patients and healthy subjects, sometimes with missing undisturbed epochs of certain sleep stages. Therefore, no repeated measures test could be applied. Prospective studies with larger patient and control groups are needed to confirm our findings. Moreover, the ability to separate between healthy and pathological regulation as well as between different severities of OSAS has to be confirmed. Recently, we showed that HRV and BPV parameters can be used to improve automatic algorithms for sleep stages classification [7]. Therefore, we are convinced that HRV, BPV and BRS will prove their diagnostic relevance in sleep medicine.

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Received February 8, 2011; accepted July 18, 2011