The aim of our study was to characterize the dynamics of heart rate variability (HRV) during sleep in healthy subjects and in patients with obstructive sleep apnea syndrome (OSAS). Present results were compared with earlier data obtained in healthy subjects (1) performing intermittent voluntary apneas. Power spectra in low (LF) and high (HF) frequency band and non linear indices: correlation dimension (CD) and recurrence plots were computed. New indices were applied: a beat-to-beat control (BBC) for the assessment of cardiovascular regulatory mechanisms as cardiac, vascular or mixed type control and COT for quantification of relative contribution of cardiac and vascular component in blood pressure variability. During Wake stage in OSAS patients mean LF component was augmented (0.035 s²/Hz) comparing to healthy subjects (0.012 s²/Hz). Nonlinear indices suggest reduced HRV dynamics complexity in OSAS patients. Similar pattern could be observed when comparing LF component, CD and recurrence parameters during spontaneous breathing and in consecutive voluntary apneas. The results correlate with 20% increase in BBC vascular control type and COT inversion form +0.08 to -0.12. Changes in BBC and COT along with power spectra and nonlinear dynamics indices appear to signal risk and/or initiation of arterial hypertension in OSAS patients.

**Key words:** cardiovascular regulation, humans, nonlinear dynamics, spectral analysis, sleep, obstructive sleep apnea
INTRODUCTION

The change in physical quantity in time, particularly if it varies around some average is defined as fluctuation. Irregular excursions from mean level are present in almost all processes. They were observed in physics, economics and biology and usually interpreted as random disturbances. Recent developments in chaos theory suggest that fluctuations could be nonrandom and play important role in the dynamics of the cardiovascular complex systems (2). The notion of equilibrium and nonequilibrium state was also revised and put into distinction between fluctuation-dependent and fluctuation-independent control mechanisms (3). There are systems which function properly without or in the presence of fluctuations and those in which presence of fluctuations is a precondition of proper function or function at all. The latter is the case in human body where fluctuations mean life, homeostasis or homeomeodynamics, while lack of them - pathology or death. Poor prognosis for cardiological patients with diminished heart rate variability (HRV) is clinically confirmed (4). Fluctuations in the frequency and time domain may reveal significant information on the dynamic characteristics lost with routine averaging or linear spectral methods. New computational techniques for the analysis of nonlinear dynamics such as correlation dimension (5), recurrence plot analysis (6), non-stationary fluctuation analysis (7), detrended fluctuation analysis (8) are useful in revealing the extent of long-range correlations in time series. We applied this approach to data analysis in two physiological situations: sleep stage dependent cardiac dynamics in healthy subjects and in patients with obstructive sleep apnea syndrome (OSAS).

Clinical data suggest that OSAS contributes to the development of systemic hypertension occurring in 60%-80% of OSAS population (9). Hypercapnia, hypoxia, arousal, swings in intrathoracic, intravascular, and intracranial pressure accompanying apneas lead to short- as well as long-time cardiovascular dynamics changes (1). Augmented responsiveness of the arterial chemoreceptor reflex contributes to sympathetic overactivity and neurogenic arterial hypertension in OSAS patients (10, 11). Episodic sleep apneas, powerful repetitive stimuli for arterial chemoreceptors, induce daytime increase in sympathetic activity and arterial hypertension in sleep apnea syndrome patients (12, 13). We have previously demonstrated that during voluntary apneas in healthy human subjects the power of slow frequency oscillations (LF) of the heart rate and arterial blood pressure (BP) computed by power spectral analysis is augmented (14), whereas chaotic behavior of cardiovascular variables is reduced (1, 15). One may hypothesized that cardiovascular control system under apneic stress should reflexively change its behavior to compensate and/or adapt to the stimulus what would translate into more or less manifested physiological parameters modification and/or shift to the new homeodynamic state. The later is of special interest, because it may help in diagnosis or assessment of risk to develop hypertension.
SUBJECTS AND METHODS

To study sleep stage dependent cardiac dynamics a group of 10 healthy volunteers and 16 OSAS patients were investigated. Healthy subjects, 5 males and 5 females, 26-51 years old (mean 38.2 SD ± 7.93) were selected after one night sleep adaptation and nocturnal oxygen saturation checking to exclude subjects with apneic periods. On the second night a standard clinical polysomnogram was performed. Sleep recordings were scored off-line by experienced rater according to Rechtschaffen and Kales criteria. Sixteen OSAS polysomnographic recordings, each with an ECG signal annotated beat-by-beat, and EEG and respiration signals annotated with respect to sleep stages and apnea were taken from the MIT-BIH Polysomnographic Database (16).

Analysis and Statistics

Data analysis based on procedures written in the 4-th generation script language of MATLAB environment and STATISTICA. Prior to the analysis time series and beat to beat data were converted to binaries suitable for MATLAB. Analog signals were preprocessed prior to digitalization and further off-line analysis. ECG signals were transformed to Spike-2 format for automatic QRS complex identification. Extra beats and artifacts were eliminated by visual inspection. The method of data segmentation and aggregation of short time series (1) was used for nonlinear and power spectral analysis. Raw R-R interval time series (IBI) were segmented according to sleep histogram and aggregated into data sets suitable for further analysis. Only uninterrupted, artifacts free, sleep stage segments longer than 100s were aggregated. Cardiovascular variables, measured during voluntary apneas, were segmented according to the respiratory signal as a reference and aggregated into four sections: control (C), aggregated apnea phase (A), aggregated inter-apnea phase (B) and recovery (R) (1).

Power spectra density estimates of discrete time signals were obtained by Welch's averaged periodogram (17). Baroreflex gain and LF/HF (2) coefficients were calculated from, introduced by authors (18), component spectra (CS). CS was evaluated as narrow band integrals around continuously traced respiratory rhythm and LF band local maxima in consecutive time slices of spectrograms.

Local maxima of power spectra were identified in the low (0.07-0.12 Hz) and high (0.12-0.35 Hz) frequency region. The differences between integrals (± 0.006 Hz around local maxima) were compared.

The two methods (18,19) enabled symbolic description of cardiovascular regulatory mechanisms as cardiac, vascular or mixed type control (BBC) and quantify relative contribution of cardiac and vascular component in blood pressure variability. The symbolic BBC procedure is classifying by Boolean or Fuzzy logic what the change of blood pressure in actual heart beat was dependent on: cardiac output (CO), total peripheral resistance (TPR) or both (MIX). Summed up for the given time interval CO, TPR and MIX type events served as indicator of control type. The inverse (INV) was used as algorithm quality coefficient, closer to zero the better beat identification. Similar to BBC but more compact index is COT (Cardiac-Over-TPR). This is normalized coefficient indicating what changes (fluctuations) of mean blood pressure are dependent on cardiac output or total peripheral resistance. If COT is +1 all BP changes are CO dependent, if COT is -1 all BP changes are TPR dependent.

Nonlinear dynamics was evaluated in time series by independent algorithms: correlation dimension - CD (5) and recurrence plot strategy (6).

Means, standard deviations (SD) and standard errors (SE) were estimated for whole set of each calculated parameter. Running average (1 minute window) and running standard deviation over time of registration for all subjects were determined by means of standard MATLAB procedures (20).

Difference in means was investigated by t-test for correlated samples at significance level 0.05 considering possible inhomogeneity of variance (21).
RESULTS

Power spectra

For healthy subjects challenging voluntary apneas, mean LF and HF components of HRV power spectral densities were equally distributed during control and LF was dominating in systolic (SYS) and diastolic (DIAS) blood pressure. During recovery in all signals there was distinguished power increase in LF region (Fig. 1).

Simple averaging however masked the true dynamics of the process. Time dependent averages revealed trends in all considered frequency bands. Successive increase in LF spectra component for apnea and inter-apnea period and decrease in HF component is clearly visible in Fig 2. In the apnea periods, when there was an increase of sympathetic activity, BRS significantly decreased, and during inter-apneas BRS increased. Similar changes were observed in LF/HF index, although significant increase in this coefficient was still present for recovery phase (Fig. 3).

The main difference between healthy subjects and OSAS patients were observed for Wake state. In the OSAS patients LF component was augmented

![Fig. 1. Average ±S.E. relative amplitudes of LF and HF spectra components of interbeat interval IBI, systolic SYS and diastolic DIAS blood pressure signals during control (C), apnea (A), inter-apnea (B) and recovery (R) for voluntary apnea challenging group (1).](image-url)
Comparison to simulated apnea in healthy subjects is hardly possible due to signal segmentation in patients according to sleep histogram and not to apnea period. Power spectra for sleep stages were alike for both healthy subjects and OSAS patients (Fig. 4).

**COT and BBC**

Long term COT analysis for the whole population suggested, that repetitive apneas led to significant increase of the vascular component in blood pressure changes. COT remained still augmented during inter-apnea periods and recovery (Fig. 5).

BBC analysis showed, that about 50% of blood pressure variability depended on vascular and 30% and 20% on heart and mixed type regulation, respectively. During apnea and inter-apnea periods vascular component reached 70% and remained on the higher level during recovery period in comparison to the control (Fig. 6). Neither COT nor BBC computing was possible in OSAS patients due to lack of blood pressure measurements.
Correlation dimension and recurrence plot analysis

For the group of healthy subjects challenging voluntary apneas results of nonlinear analysis were already published (1, 22) and here they have been briefly

Fig. 3. Average LF/HF Index during control C, Inter-apnea periods B and recovery R. An asterisk denotes statistical significance at $\alpha < 0.05$. Analysis based on data from (1).

Fig. 4. Mean power spectra of aggregated interbeat interval for normal subjects (dotted line) and OSAS patients (solid line) during four sleep stages - WAKE, Stage S1&2, Stage 3&4 and REM.

Correlation dimension and recurrence plot analysis

For the group of healthy subjects challenging voluntary apneas results of nonlinear analysis were already published (1, 22) and here they have been briefly
recalled. Correlation dimensions computed from time series of all cardiovascular variables were reduced during apnea versus control and recovery. Correlation dimensions of aggregated inter-apnea time series were significantly reduced only for cardiac output and total peripheral resistance. All variables had a significantly lower correlation dimension during aggregated apneic periods than CD for inter-apnea aggregated free breathing phases. Except of interbeat interval CD of all cardiovascular variables was lower during inter-apnea periods than during recovery period. However the difference was significant only for systolic blood pressure and stroke volume. Respective mean values for the ratio (ibid) of %determinism versus %recurrence (RDR) were significantly augmented for time series of all cardiovascular variables during aggregated apneic periods compared to control.

Fig. 5. Whole population averages +/- S.E. of COT coefficient during control C, apneas A, inter-apneas B and recovery R. NS denotes lack of the statistical significance at $\alpha < 0.05$. Analysis based on data from (1).

Fig. 6. Results of BBC analysis for the whole population, Mean +/- S.E. percent of cardiac CO, vascular TPR, mixed MIX and invers INV type of regulation during control C, apnea A and inter-apnea B intervals and recovery R. NS denotes lack of statistical significance at $\alpha < 0.05$. Analysis based on data from (1).
Augmentation of RDR of total peripheral resistance outlasted significantly apneic and inter-apnea periods and was still enhanced during 10 min of recovery.

There are evident differences in heart rate dynamics between normal subjects and OSAS patients both in WAKE as well as REM sleep stages as shown in recurrence plots (Fig. 7).

Quantitative dynamics differences were described by percent recurrence (%R) and CD. The former are substantial lower for all sleep stages but REM sleep in OSAS group (Fig. 8), whereas opposite relation exists for correlation dimension, which is significantly higher in WAKE and S1&2 stage. Correlation dimension of aggregated cardiac R-R intervals significantly increased in WAKE and S1&2 stage, did not significantly change in S3&4 and REM sleep whereas (%R) significantly decreased in WAKE, S1&2 and S3&4 stages but increased in REM sleep (Fig. 8), % determinism increased in S3&4 and REM sleep in OSAS patients as compared to healthy subjects.

**Descriptive statistics**

Standard deviation (SD), a linear time domain measure of variability of all cardiovascular variables was slightly yet significantly augmented during
aggregated apneas compared to control resting period except of SD of inter-beat intervals (IBI). However SD of IBI values was also augmented significantly in the aggregated inter-apnea periods. There were no significant changes for variability of the rest of parameters but TPR, which was the highest during apnea and successively decreased but reminded still higher in the inter-apnea and recovery period. No differences in the heart rate variance computed for the same sleep stages were observed between normal subjects and OSAS patients.

**DISCUSSION**

The two models have been chosen to study cardiovascular function: obstructive pathological and nonobstructive voluntary recurrent apneas. We compared standard statistical measures, such as means and variances, to time frequency transform and nonlinear methods. Our results suggest that in some cases application of linear coefficients to study variability changes failed in differentiation between distinct system states. Variance of the most cardiovascular parameters did not change significantly between aggregated apnea-inter-apnea

![Fig. 8. Comparison of mean %recurrence in NORMAL subjects and OSAS patients in different sleep stages.](image)
and control-recovery period in healthy subjects during voluntary breath hold challenge. There were also no clear variance differences for the same aggregated sleep stages between healthy subjects and OSAS patients. In spite of the evident discrepancy between time course of the signals in experiment phases the lack of mean and variance differences could be explained by mean and variance insensitiveness to time course of changes. Both coefficients would be similar for original data and their surrogates.

More informative were results of standard power spectra for IBI, SYS and DIAS. The time frequency analysis revealed a trend in spectral components, which is novel observation. Heart rate fluctuations depends on sinus node efferent autonomic nerve activity and humoral influences. It is represented as energy concentration in high frequency (HF), almost entirely related to rhythmical respiratory vagal activity modulating heart rate and breathing movements modulating blood pressure, and in low frequency (LF ~ 0.1 Hz) spectra regions of heart rate and blood pressure variability signals (HRV and BPV respectively). Coincidence of sleep apnea and hypertension as an independent risk factor, leads to an assumption on similar spectral distributions of HRV and BPV signals in patients with obstructive sleep apnea syndrome (OSAS) and hypertension. HRV and BPV spectral analysis in patients with primary hypertension and genetic predisposition to hypertension demonstrated power increase in LF, decrease in HF region and decrease of baroreflex gain (22). Similarly cardiorespiratory changes induced by periodical apneic stimulus could be reflected in the power spectra of registered signals and/or basic hemodynamic parameters variability. The difference in LF power of IBI signal between healthy subjects and OSAS patients in WAKE appears to confirm this hypothesis. Patients with established OSAS might have power spectra pattern similar to hypertensive patients. However, power spectra estimated for aggregated sleep stages did not show differences. There might be few reasons of that result. First of all, groups were not matched. Second, process of aggregation by sleep stages cumulated mixed apnea and non-apnea data into one, continuous time series. Routine periodogram averaging (17) could smooth LF peaks related to apnea events. Moreover mean sleep stage timing in OSAS patients differs significantly from healthy subjects. Aggregated WAKE and S1 stage are respectively 8 and 4 times longer in OSAS patients whereas S2, S3, S4 and REM stages are due to arousals accompanying apneas shorter than in healthy subjects. Third, linear predictors such as power spectra may be not suitable for identification of this kind, subtle dynamics changes. In healthy subjects challenging voluntary apneas mean LF and HF components of HRV and BPV power spectral densities were equally distributed during control and LF was dominating in SYS and DIAS. During recovery, in all signals there was distinguished power increase in LF region, which may suggest sympathovagal balance change to the direction of the sympathetic predominance (23). Similar changes were observed in LF/HF index.
In the apnea periods, when there was expected an increase in sympathetic activity, BRS significantly decreased, and increased again during inter-apnea periods. This result is in accord with data reported by other researchers. Leuenberger and colleagues (24) studying sleep apnea patients recorded muscle sympathetic nervous activity (MSNA) during spontaneous apneas and during apneas in which oxygen supplementation completely abolished desaturations. MSNA decreased with oxygen supplementation as did the change in arterial pressure during the apnea-recovery cycle. Katragadda (25) was investigating MSNA during sustained Mueller maneuvers, intermittent Mueller maneuvers, and simple breath holds in six healthy humans before, during, and after ganglionic blockade with trimethaphan. Ganglionic blockade abolished sympathetic bursts from the neurogram and eliminated pressor response to sustained and intermittent Mueller maneuvers and breath holds. This result strongly support conclusion that the acute pressor response to voluntary apnea is sympathetically mediated.

Analysis in frequency domain performed in time sequence apnea by apnea revealed information masked by overall averaging of aggregated spectral components. We identified a linear trends in low and high frequency regions. LF spectral component during apnea and inter-apnea periods is increasing and HF component during inter-apnea periods is decreasing with every consecutive apnea. Magnitude of cardiovascular oscillations during each apnea appears dependent upon previous or even earlier apnea period. Such long lasting facilitatory effect may be of significance in OSAS patients who experience hundreds apneas a night. Increase in LF component, related to sympathetic activity fluctuations, could be induced by repeatable, combined hypoxic and hypercapnic excitation (18). Combined hypoxia and hypercapnia causes a substantial MSNA increase that outlasts the chemical stimuli (26). Sustained activation of the sympathetic nervous system may be associated with the elevated blood pressure in the subjects with preclinical sleep-disordered breathing as well as in OSAS patients.

In order to study non-linear properties and chaotic behavior of the cardiovascular control system during apnea in humans the method of dynamics dependent windowing and data aggregation procedure was introduced. The results of CD and RDR estimation suggest that within apnea itself the complexity of the cardiovascular control system is reduced. This is probably due to antagonistic interaction between baroreceptor (cardioinhibitory) and chemoreceptor sympathoexcitatory reflex (1). Attenuation of baroreceptor reflex by augmented peripheral chemoreceptor reflex drive could account for reduced complexity of the cardiovascular control system during apnea. It has been suggested that obstructive sleep apnea syndrome triggers a chemoreceptor reflex mechanism close to that which contributes to primary hypertension (10). Voluntary apnea differs from obstructive sleep apnea. Both of them induce however similar cardiovascular reflex responses (27). It may justify an application of the former for investigation of the risk of sustained hypertension.

CD is good differentiator of sleep stages within one group but is less effective to between groups comparison. It shows, however, clear distinction between healthy
subjects and OSAS patients as to the complexity changes during sleep stages. An excellent differentiator for both within and between group quantification is % recurrence (%R). Heart interval dynamics in healthy subjects is more complex (increased %R) in all stages but REM than in OSAS patients. Dynamics of heart intervals is more complex during sleep, except of healthy subjects in REM stage.

We found a difference in percent recurrence of heart interval dynamics between healthy subjects and OSAS patients in WAKE and REM sleep stage. Increased complexity of heart interval dynamics during REM in OSAS patients may be related to more numerous apneic events in this stage.

BBC and COT analysis were performed during voluntary apnea using original measurements presented in our previous study (1, 15). In control there were similar participation of CO and TPR in the blood pressure regulation. During apnea CO and MIX decreases and TPR increases and remains elevated during inter-apnea and recovery periods. In the group of healthy subjects mean COT value was positive during control (0.08), what means that blood pressure fluctuations were in about 10% more of cardiac than of vascular origin. During apnea and inter-apnea intervals COT value is negative, a finding indicating a vascular, TPR related origin of blood pressure changes. Such vascular pattern of blood pressure control was preserved during recovery period after repetitive apneas. We confirmed our previous results (1, 15) that brief repeatable voluntary apneas in young, healthy persons induce long lasting cardiovascular aftereffects such as arterial pressure elevation and changes in blood and heart rate fluctuations and in hemodynamic parameters. Arterial blood pressure, total peripheral resistance and heart rate low frequency fluctuations (LF), as well as changes of BBC and COT coefficients suggest that repeatable apneas induce persisting neurogenic mechanism related to sympathetic activation. Reduction of the correlation dimension (CD) and increase in ratio (RDR), the indices of nonlinear dynamics of the arterial blood pressure, heart rate and other cardiovascular variables suggest a reduced complexity of cardiovascular control system exposed to apnea and chemoreceptor stimulation. Reduced complexity of the circulatory control system may be related to temporary inhibition of some regulatory feedback loops, possibly baroreceptor inhibitory reflex. In conclusion the results of present study suggest that changes of hemodynamics detected by the applied indices and procedures may be considered as a potential markers signaling risk and/or initiation of arterial hypertension in OSAS patients.

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