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CLINICAL STUDY

Heart rate variability in hypertension caused by sleep disordered breathing and its modification by CPAP

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Abstract: *Objectives:* 1) To analyze heart rate variability (HRV) changes, reflecting the sympathovagal balance with secondary hypertension caused by sleep disordered breathing (SDB), compared to healthy controls and essential hypertension without SDB; 2) to compare HRV changes between various degrees of SDB severity; and 3) to test the modification of HRV indices by continuous positive airway pressure (CPAP) in SDB patients.
Background: Differentiation of secondary hypertension caused by SDB from essential hypertension and healthy controls by ambulatory blood pressure measurement (ABPM) and its modification by CPAP, requires an analysis of HRV changes, as frequently used for the prediction of cardiovascular risk.
Methods: HRV changes were analyzed in 48 adults divided into six groups according to the apnoea/hypopnoea index (AHI), i.e. three groups with various degrees of SDB, a group with severe SDB after CPAP application, a group with essential hypertension without SDB, and a group of healthy controls. Night-time and daytime values of low frequency (LF) and high frequency (HF) bands and the LF/HF ratio were compared in the six groups.
Results: The night-time values of LF bands were higher in severe than in moderate and mild degrees of SDB, and the correlation of LF/HF ratio with AHI (r=0.3511) suggests the gradual increase of sympathetic predominance with the severity of SDB. The high sympathetic activity substantially decreased after application of CPAP in severe SDB.
Conclusion: The increased nocturnal values of the LF band and the LF/HF ratio, caused by frequent apnoea/hypopnoea episodes, support the usefulness of HRV spectral analysis for the prediction of cardiovascular risk in patients with SDB *(Tab. 1, Fig. 3, Ref. 36)*. Full Text in free PDF *www.bmj.sk.*
Key words: cardiovascular risk, hypertension, heart rate variability, sleep disordered breathing, spectral analysis.

Abbreviations: AHI – apnoea/hypopnoea index, ANS – autonomic nervous system, ABPM – ambulatory blood pressure measurement, BP – blood pressure, CPAP – continuous positive airway pressure, HF – high frequency component of spectral heart rate analysis, HRV – heart rate variability, LF – low frequency component of spectral heart rate analysis, OSAHS – obstructive sleep apnoea/hypopnoea syndrome, SDB – sleep disordered breathing.

Sleep disordered breathing (SDB) represents a risk factor for development of secondary arterial hypertension, often resulting in cardiovascular morbidity and mortality (1–6). In subjects with suspected SDB, admitted to a sleep laboratory for polysomnographic examination, considered by some as a gold standard for detection of SDB, hypertension was detected in 39 % by occasional blood pressure (BP) measurements and in 62 % by non-invasive ambulatory BP monitoring (ABPM) (7, 8). Therefore, ABPM was proposed for all subjects with suspected SDB (6–9). In addition, non-invasive heart rate variability (HRV) analysis was developed as a screening tool for the obstructive sleep apnoea/hypopnoea syndrome (OSAHS) (10–17), instead of time-consuming and expensive whole-night polysomnography. This relatively simple method has been extensively used for prediction of the imminent risk of cardiovascular complications, including sudden cardiac death, e.g. in heart failure (18–20), myocardial infarction (5, 21, 22), and stroke (23, 24), and to study cardiac arrhythmias (25-27), the mechanisms of sympathovagal balance (14, 16, 28–30) and the effects of continuous positive airway pressure (CPAP) (31–33).

Our previous study with 24-h ABPM and parallel whole-night polysomnographic examination, performed on 116 adult subjects in a sleep laboratory, allowed differentiation of secondary hypertensive patients, manifesting with SDB (apnoea/hypopnoea index (AHI) > 5/h sleep) and essential hypertension without SDB (AHI < 5/h), as well as from clinically healthy control subjects (6). The severity of SDB characterized by AHI, duration of hypoxemia with $SaO_2 < 85$ %, minimal SaO_2, and a decrease of average SaO_2, correlated with the increase in the average night-time diastolic blood pressure, appearing as the first

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sign of secondary hypertension. This "dose-dependent" nocturnal secondary hypertension was improved after application of CPAP (6), similar to that observed in drug-resistant hypertensive patients, mostly suffering from SDB (2, 33).

The 'non-dipping', or even a moderate increase in blood pressure during sleep in patients with SDB, caused by a strong sympatho-adrenergic effect, and the improvement of hypertension after application of CPAP in severe SDB, required testing for HRV, reflecting the changes in autonomic nervous system (ANS) activity. Therefore, the aims of the present study, which extends the results of our previous paper (6) are as follows: 1) comparison of the HRV changes in adults with secondary hypertension caused by SDB with essential hypertension and with the changes in control healthy subjects; 2) comparison of the HRV changes between the various degrees of SDB severity; and 3) to test the modification of HRV indices in patients with severe SDB after application of CPAP. The ECG records were obtained by 24 h ABPM and other relevant data from parallel overnight polysomnography.

Methods

Polysomnography

An overnight sleep study was performed between 22.30 and 06.00 h in each of 48 selected subjects in a sleep laboratory using the Alice 3 device (Respironics, Murryswille, PA), under the supervision of a skilled technician. All subjects signed an informed consent form and the Ethics Committee of the Faculty of Medicine, UPJS Kosice, approved the protocol. Nasal and oral airflows were monitored by a thermistor, or oro-nasal cannula, and laryngeal sounds by a microphone. In addition, the second lead of an ECG, two classical electroencephalograms (C3A1, C4A2) and right and left electro-oculogram recordings were also included. Submental and lower limb electromyograms were continuously recorded, using surface electrodes, together with chest and abdominal movements by belts connected to a strain gauge, as well as various parameters of arterial oxygen saturation by a finger pulse-oximeter. The data were stored on a computer, and the software automatically calculated over 20 parameters, including AHI (for more details see 6).

Sleep parameters were scored according to standard criteria (34). Hypopnoea was defined as a reduction in airflow by 50 % for at least 10 s. Apnoea was diagnosed when respiratory flow was reduced to <20% of the baseline values for at least 10 s. The absence of chest and abdominal wall movements indicated a central type of apnoea or hypopnoea. The chest and abdominal movements identified the obstructive type of apnoea or hypopnoea, resulting from upper airway occlusion and ineffective respiratory efforts. The AHI was defined as the number of episodes of apnoea and hypopnoea per hour of sleep. Increased AHI was associated with oxyhaemoglobin desaturation of 3% or more, possibly followed by an arousal from sleep.

Blood pressure recording and heart rate variability analysis

All subjects were studied using overnight polysomnography in the sleep laboratory. BP and ECG were simultaneously monitored, using a device (Cardiotens 0.1, Meditech, Budapest) specially designed for ABPM and HRV analysis, during a 24-h period on a normal workday (6). For more detailed analysis, the data for the night were collected from 4-h periods for comparison of the nocturnal with daytime data. The records were obtained from the period between 00.00 and 04.00 h, when REM sleep stages are more frequent and often contribute to ventilatory and respiratory disorders as well as cardiovascular complications, including sudden cardiac death. REM sleep is characterized also by increased prevalence of the low frequency (LF) spectral component of HRV, linked to the higher sympathetic modulation and with the highest low frequency/high frequency (LF/HF) spectral ratio even in healthy subjects (35). The data for the day were collected from the records obtained between 08.00–12.00 h, a period characterized by the usual morning stresses.

HRV was assessed in the same 4-h periods from the 24-h ECG recordings, after full revision of the ECG and editing the data when required. 48 adult subjects were selected from a larger number of persons investigated in the sleep laboratory, for technical reasons and because of limitations in the method; some clinical disorders, e.g. tachyarrhythmias, previous myocardial infarction, stroke and chronic heart failure, may present technical problems and may cause a blunted reactivity of the ANS, and are often associated with SDB. Therefore, we excluded from the study patients with these disorders and those with failure of various vital organs.

During the analysis, all recording artefacts and atrial fibrillation, or more than 15 % of premature ventricular beats, precluding frequency domain analysis, were eliminated. The frequency spectra were determined for the period of sleep versus wakefulness using spectral analysis and fast Fourier transform, concentrating on three main indices of HRV: 1) HF oscillations (0.15–0.4 Hz), connected with respiratory activities mediated by the vagus nerves and indicating increased parasympathetic activity; 2) LF oscillations (0.04–0.15 Hz), reflecting mainly the baroreflex control of BP, and indicating sympatho-adrenergic activation; and 3) LF/HF ratios expressing momentary sympatho-parasympathetic balance. In addition, an approximate 24 h total power was calculated as a sum of daytime LF/HF ratios (over 14 h of wakefulness on average) + nocturnal LF/HF ratio (over 7 h sleep on average), to assess the general involvement of the ANS in the six analyzed groups. Heart rate mainly depends on vagal activity, but it is frequently influenced by both central and peripheral mechanisms (activity of the cardio-respiratory centres and peripheral effects of BP and breathing). One of the main goals of this study was to assess and compare the activity of the ANS for a selected, mostly stressful and informative 4-h period of sleep, versus a daytime 4-h period of wakefulness with usual morning stresses. To the best of our knowledge, this is one of the first studies: 1) to monitor the acute changes in HRV with a parallel overnight polysomnographic recording, performed in a sleep laboratory; 2) to compare the nocturnal indices of HRV with the corresponding daytime values; 3) to differentiate the HRV changes in secondary hypertension caused by SDB from those in essential hypertension and control subjects; 4) to simulta-

Tab. 1. Distribution of subjects with their anthropometric data, selected BP and HRV values, severity of SDB, and data after CPAP application.

Group / Parameter	Control group	Essential AH	Mild SDB (5<AHI?20/h)	Moderate SDB (20<AHI ?40/h)	Severe SDB (AHI>40/h)	Severe SDB after CPAP
n-number of subjects	8	9	11	8	7	5
Age (yrs)	48,1±18,3	56.2±13,3	53,3±10,6	52,5±10,7	50,5±9,6	47,1±4,8
BMI (kg/m^2)	26,5±3,2	30,0±5,3	29,9±3,8	33,3±6,9	35,2±6,4	36,2±7,7
AHI/h	2,3±1,7	2,9±1,0	9,1±2,5	31,4±6,3	58,0±8,1	10,2±5,0
Night-time SBP(mm Hg)	112±9,0	●●● 136±11,9	+ 122±12,8	127±16,5	●●● 135±15,5	●●+ 133±13,7
Night-time DBP (mm Hg)	63±9,5	● 73±5,9	70±8,6	71±8,1	●●●xΔ 80±8,7	●●+x 80±4,6
Daytime SBP (mm Hg)	121±12,5	●● 151±22,8	●+ 133±9,5	●●+ 135±8,7	● 147±18,7	●●● 138±7,7
Daytime DBP (mm Hg)	73±11,7	88±14,3	82±7,5	82±5,5	●xΔ 93±10,1	# 81±1,6
n. log LF/HF ratio ± SD	0,95±0,6	0,6±0,9	0,61±0,67	0,74±0,75	x 1,53±0,6	0,7±0,6
d. log LF/HF ratio ± SD	1,1±0,6	1,2±0,9	0,9±0,7	1,4±0,8	1,7±0,9	1,5±0,7
Aprox. 24h. Total power n+d log LF/HF	25,3	24,6	19,6	29,0	Δ 39,6	30,4
n. log LF vs.d. log LF	0,98	1,02	1,08	1,05	■ 1,24	1,02
n. log HF vs.d. log HF	1,02	■ 1,13	1,18	■ 1,23	■ 1,35	1,19
n. log LF/HF ratio vs. d. log LF/HF ratio	0,86	0,5	0,68	0,53	0,9	■ 0,47

Means ± SD of measured parameters: Age – years, BMI – Body Mass Index (weight-kg)/(height-m)^2), SBP – systolic blood pressure, DBP – diastolic blood pressure, n. log LF/HF ratio – night-time log low frequency/high frequency band ratio, d. log LF/HF ratio – daytime log low frequency/high frequency band ratio. Aprox. 24h Total power calculated as a sum of night-time LF/HF ratio x 7h of sleep + daytime LF/HF ratio x14h of wakefulness. Significant differences of each indicated value of the selected group compared to other 5 groups are indicated by various symbols: ● – vs. healthy controls, + – vs. AH, x– vs. mild SDB, Δ – vs. moderate SDB, and # – vs. severe SDB, n. log LF vs. d. log LF (night-time vs. daytime values of the low frequency bands), n. log HF vs. d. log HF (night-time versus daytime values of high frequency bands), n. log LF/HF ratio vs. d. log LF/HF ratio (night-time log low frequency/high frequency ratio vs. daytime log low frequency/high frequency ratio). ■ comparison of night-time with daytime values of LF, HF bands and LF/HF ratios separately. The level of significance is indicated by the symbol ($p<0.05$) in the pertinent groups.

neously test the acute antihypertensive effect of the application of CPAP on the HRV indices in SDB; and 5) to compare the involvement of the ANS and the approximate general loading of the subjects in analyzed conditions.

Statistics

Forty-eight subjects were enrolled and subdivided into six groups according to AHI indicating the severity of SDB, presence or absence of hypertension, and application of CPAP. The most sensitive parameters of ABPM, detecting the early signs of secondary hypertension, and proposed for screening of SDB (6), were compared to the changes in HRV indices. The results are expressed as means ± SD. Analysis of the six subgroups according to the presence or absence of hypertension and the presence and severity of the SDB, as well as the treatment of a severe SDB group by CPAP, were performed by the Mann-Whitney test. Data analysis was carried out using the SDSS statistical programme Arcus Quickstat (Biomedical).

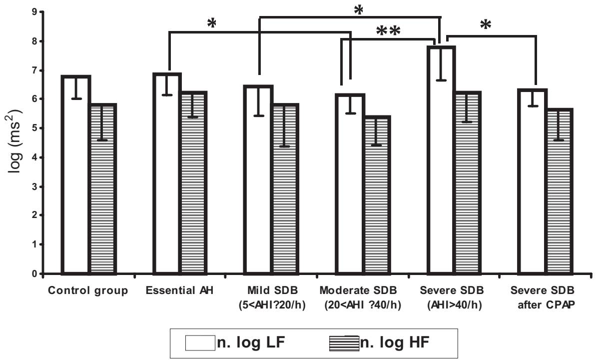

Fig. 1. Comparison of nocturnal values of LF and HF bands between the corresponding groups.

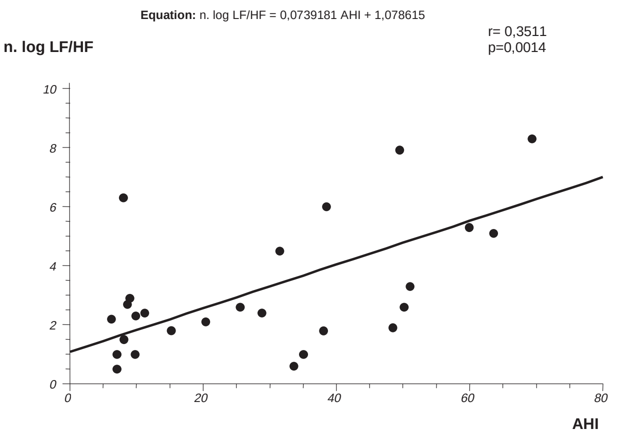

Fig. 2. Correlation of n. LF/HF ratio with AHI in three groups of patients with SDB.

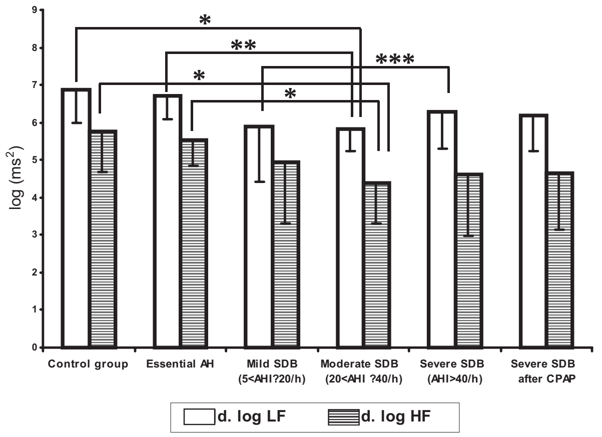

Fig. 3. Comparison of daytime LF and HF values between the corresponding groups.

Results

The main characteristics of the 48 subjects show no significant differences in age and body mass index (BMI) between the separate groups (Tab. 1). However, for selection criteria, there are substantial differences in AHI between the healthy controls and patients with essential hypertension (AHI<5/h) and patients suffering from SDB (AHI>5/h). There are also differences in BP values, analyzed in more detail on 116 adults with similar results in our previous paper (6). The individual use of various antihypertensive drugs and their combinations was not changed during this study, or in the previous one.

HRV analysis, illustrated in Figs. 1-3 and listed in Table 1, indicates the following main results: 1) the values of nocturnal LF band are higher in patients with severe than in those with moderate (p<0.01) and mild (p<0.05) SDB, but they are significantly decreased in severe SDB after application of CPAP during sleep (p<0.05). However, the nocturnal LF band has lower values in patients with moderate SDB (p<0.05) than in essential hypertension (Fig. 1); 2) in patients from three groups of SDB the night-time LF/HF ratio highly correlates with AHI (r=0.3511), indicating that the predominance of sympathetic tone increases with the severity of SDB (Fig. 2); 3) patients with moderate SDB have lower daytime values of LF band than the control subjects and the patients with essential hypertension (both p<0.05), but higher in severe than in mild SDB (p<0.001). The daytime values of HF band are significantly lower in moderate SDB compared not only to patients with essential hypertension (p<0.01), but also to control subjects (p<0.05), and they have a tendency to decrease also in mild and severe SDB (Fig. 3). This is similar to observations of depressed waking vagal tone independent of sympathetic activation in SDB (36). 4) Results in the Table 1 indicate, that the nocturnal LF/HF ratio is higher in patients with severe compared with mild SDB (p<0.05), but tends to decrease markedly after application of CPAP in severe SDB and in patients with essential hypertension spontaneously, during the night, suggesting lowering of sympathetic predominance in both conditions. The daytime values of log LF/HF ratio show only nonsignificant differences between the separate groups. The approximate 24 h total power indicates higher values in severe than in mild SDB (p<0.05), reflecting the severity of the cardio-respiratory loading, in agreement with the observation that untreated OSAHS increases the severity rather than the prevalence of complications (5). Comparison of the night-time with the daytime parameters indicates that in patients with SDB both the LF and the HF bands have higher values during the night; therefore the night-time/daytime ratio is higher, particularly in severe SDB (p<0.05), documenting sympathetic predominance during sleep. On contrary, in subjects without SDB, after elimination of apnoe/hypopnoe episodes by CPAP, the sympathetic predominance decreases and this ratio is around 1. The nocturnal values of LF/HF ratio are higher than during the day not only in severe and moderate SDB, but also in essential hypertension (all p<0.05), indicating an increased parasympathetic tone. Therefore, the nocturnal values of LF/HF ratio, compared to its daytime values are practically without significant changes, with exception of the group after CPAP, eliminating the nocturnal sympathetic predominance (Tab. 1).

Discussion

‘We have previously shown (6) that: 1) SDB causing marked hypoxemia induces secondary hypertension, manifesting with a “dose-dependent“ increase in nocturnal rather than in daytime diastolic and systolic BP; 2) the nocturnal diastolic BP, which is the first sign of secondary hypertension, correlated with AHI and the duration of SaO_2 below 85 %; 3) secondary hypertension in patients with severe SDB was significantly lower after application of CPAP; 4) ambulatory monitoring of the diastolic BP and some other parameters, proved to be useful for detection of secondary hypertension and its control in patients with SDB.

The present study extends these observations in the following ways: 1) the nocturnal values of LF band are significantly increased in patients with SDB; 2) the nocturnal values of LF/HF ratio, reflecting sympathovagal balance, gradually increasing from mild to severe SDB, closely correlate with the AHI, which confirms the strong and gradually increasing sympathetic activation during sleep in patients with SDB; and 3) the strong sympathetic hyperactivity in patients with severe SDB was markedly reduced by application of CPAP. However, the subsequent daytime values of LF/HF ratio indicate only a moderate decrease, reflecting a small reduction of daytime sympathetic tone, probably supported also by parallel depression of daytime vagal tone observed in SDB (36). Also, the daytime values of LF/HF ratio tend to increase with the increasing severity of SDB.

At least two pathogenic mechanisms seem to be involved in the development of the secondary hypertension and parallel changes in HRV indices in the frequency domain caused by SDB: 1) hypoxemia reflected by significant increases in AHI, duration of SaO_2 below 85 % and a decrease in SaO_2 %, which were eliminated after application of CPAP in SDB; and 2) arousal-related acute reflex effects suggesting symphatho-adrenal activation manifested mainly by increases in nocturnal rather than persistent daytime systolic and diastolic BPs, as well as in nocturnal HRV indices, compared to daytime ones. These reflex effects manifesting with vasoconstriction and changes in heart rate could prevail in the lowest degree of SDB with AHI 5-10/h, characterized as habitual snoring and upper airway resistance syndrome, or respiratory effort-related arousal, where hypoxemia is not severe enough to provoke frequent respiratory events and higher AHI. Graded scoring of 5-min periods of the sleep stages indicated that the signs characterizing REM and slow wave sleep, appear in the EEG only after the cardio-respiratory events (35). These findings agree with the various degrees of arousal (mini-arousal <3s, arousal 3-15s, and macro-arousal >15s), following sighs, gasps and gasping respiration.

Our previous study (6), which analyzed the results of ABPM and parallel whole-night polysomnography, allowed the screening of both SDB and hypertension and detection of BP parameters indicating early signs of secondary hypertension caused by SDB and its distinction from other types of hypertension, as well as the acute effects of CPAP therapy of SDB on BP values (6). These effects reflect the influence on sympathetic and parasympathetic components of the ANS, and manifest also the changes of HRV indices, analyzed in the present paper. 3) correlation between the severity of obstructive sleep apnoea (OSAHS) and changes in heart rate indicate that the frequency domain indices tend to reveal the difference between the moderate and severe groups better than the time-domain indices (6, 14, 17). In particular, the nocturnal LF/HF ratio correlated best to the AHI, reflecting the severity of SDB. Our previous (6) and present results confirm and extend this conclusion to milder degrees of SDB. Our results confirm also the high values of nocturnal LF/HF ratios with a strong immediate decrease of sympathetic hyperactivity after application of CPAP therapy (compared to daytime LF/HF ratio). Our results also agree with the observation that in the patients with heart failure, the nocturnal LF/HF ratio was bigger in severe OSAHS, than in controls (12).

The relatively small number of subjects in separate groups, together with the use of the anti-hypertensive or other medicaments, may limit the statistical significance of the observed changes, however, our results suggest that the strong sympatho-adrenergic activation during sleep in patients with SDB can manifest itself not only in a dose-dependent increase of BP but also by marked changes in sympatho-vagal tone, reflected by changes in indices of HRV, persisting partially into the daytime. Therefore, ABPM and HRV analysis are useful methods for detection of secondary hypertension and marked changes in sympathovagal balance, applicable also for the prediction of cardiovascular risk in suspected patients for SDB.

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