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Heart rate autonomic regulation in hypertensive patients with obstructive sleep apnea syndrome

V. V. Shchekotov, E. A. Luchnikova, P. N. Barlamov

Perm State Medical University named after Academician E. A. Vagner, Perm, Russia

Corresponding author:
Vladimir V. Shchekotov,
Perm State Medical University n.a. Academician E.A. Vagner, 68 B. Gagarin street, Perm, 614077 Russia.
Phone: +7(342)263–43–99.
E-mail: healthpro@mail.ru

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Abstract

Objective. To analyze peculiarities of heart rate autonomic regulation in patients with hypertension and obstructive sleep apnea (OSA) at rest and during active orthostatic test (AOT). **Design and methods.** The study involved 65 patients, average age — 53.7 ± 10.1 years. The complex examination included anthropometric parameters measurement, cardiopulmonary monitoring (CPM), and analysis of heart rate variability (HRV) at rest and during the AOT. **Results.** The group 1 included 26 people with mild-to-moderate OSA, the group 2 consisted of 39 patients with severe OSA. In group 1 sympathetic influences on the heart rate regulation were predominant, and very low frequency (VLF) waves made a significant contribution in the overall spectrum. Key indicators of the CPM had no effects on HRV in group 1. In group 2, the severity of respiratory disorders directly affected the heart rate: low frequency (LF) waves and the LF/HF index, while high frequency (HF) waves reduced along with the increase in OSA severity. In group 1, the total capacity of the spectrum increased due to a larger contribution of LF-waves and VLF-waves during the AOT. The LF/HF index increased during the AOT. In group 2, there was a paradoxical increase in HF-waves, and a decrease in LF/HF index. **Conclusions.** The autonomic regulation of the heart rate is disturbed in hypertensive patients with OSA. Excessive sympathetic activation occurs as OSA severity increases, manifesting as the rise of VLF and LF-waves proportion and being the most profound in patients with severe OSA.

Key words: obstructive sleep apnea syndrome, hypertension, heart rate variability

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Особенности вегетативной регуляции сердечного ритма у больных гипертонической болезнью с синдромом обструктивного апноэ во время сна

В. В. Щёкотов, Е. А. Лучникова, П. Н. Барламов

Государственное бюджетное образовательное учреждение высшего профессионального образования «Пермский государственный медицинский университет имени академика Е. А. Вагнера» Министерства здравоохранения Российской Федерации, Пермь, Россия

Контактная информация:
Щёкотов Владимир Валерьевич,
ГБОУ ВПО «ПГМУ им. акад. Е. А. Вагнера» Минздрава России, ул. Б. Гагарина, д. 68, Пермь, Россия, 614077.
Тел.: +7(342)263–43–99.
E-mail: healthpro@mail.ru

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Резюме

Цель исследования — проанализировать особенности вегетативной регуляции сердечного ритма у пациентов гипертонической болезнью (ГБ) с различной тяжестью синдрома обструктивного апноэ во время сна (СОАС) в покое и при проведении активной ортостатической пробы (ОСП). **Материалы и методы.** Обследовано 65 больных ГБ, средний возраст — 53,7 ± 10,1 года; из них — 26 человек с СОАС легкой и средней степени тяжести (группа 1) и 39 человек с тяжелым СОАС (группа 2). В комплекс обследования входило определение антропометрических показателей, проведение кардиопульмонального мониторирования (КПМ), анализ вариабельности ритма сердца (ВРС) в покое и при проведении ОСП. **Результаты.** В группе 1 выявлено преобладание симпатических влияний в регуляции сердечного ритма, а также значительный вклад волн очень низкой частоты (VLF — very low frequency) в общий спектр. Основные показатели КПМ в этой группе не влияли на показатели ВРС. В группе 2 выраженность нарушений дыхания во время сна прямо коррелировала с увеличением доли волн низкой частоты и коэффициента LF/HF, а также снижением доли волн высокой частоты (HF — high frequency). При проведении ОСП в группе 1 увеличивалась общая мощность спектра за счет большего вклада волн низкой частоты (LF — low frequency) и VLF-волн. Коэффициент LF/HF возрастал при проведении ОСП. В группе 2 парадоксально увеличивалась доля HF-волн в регуляции сердечного ритма. Коэффициент LF/HF уменьшался. **Выводы.** Выявлено нарушение вегетативной регуляции сердечного ритма у пациентов с СОАС. С увеличением степени тяжести СОАС происходила избыточная симпатическая активация, проявляющаяся увеличением доли VLF и LF-волн в сердечном ритме.

Ключевые слова: синдром обструктивного апноэ во время сна, гипертоническая болезнь, вариабельность ритма сердца

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Introduction

Obstructive sleep apnea syndrome (OSAS) is characterized by episodes of reduction or pauses in breathing during sleep as a result of soft-tissue collapse at the pharyngeal level, lasting more than 10 seconds and combined with reductions in blood oxygen levels. OSAS prevalence rate in males is 3–7 % and for females, 2–5 % [1]. OSAS is a common comorbid disorder in patients with various diseases such as obesity, diabetes mellitus, coronary heart disease, arrhythmias, and hypertension [2, 3].

Autonomic imbalance is an essential part of OSAS. Heart rate variability (HRV) profile is one of the easiest routine methods for assessment of the cardiovascular effects of autonomic regulation. A number of studies showed that OSAS is accompanied by the predominance of sympathetic effects on the heart rate. Besides, the severity of autonomic imbalance is directly related to the severity of OSAS. The researchers mainly focused on the full-night electrocardiogram (ECG) conducted together with polysomnography [4, 5]. There are far less data on functioning of the autonomic nervous system in the daytime. A study concerned with HRV research in the daytime showed that the severity of autonomic imbalance of the heart rate in patients with OSAS is directly related to the severity of sleep-disordered breathing. Moreover, HRV changes were not associated with hypertension or heart failure [6]. Very few studies are concerned with comparing the severity of autonomic imbalance of the heart rate regulation in patients with various severity of OSAS, and the results of these studies are inconsistent.

We assumed that apnea and desaturation episodes in the nighttime lead to the lacking autonomic regulation of the cardiovascular system during functional loads in the daytime.

Study objective is to analyze the characteristics of autonomic regulation of the heart rate in hypertensive patients with various severity of OSAS in the daytime (at rest), as well as to assess the adaptation in these patients during the tilt test.

Design and methods

Altogether 65 patients with hypertension were enrolled in our study including 8 persons (12.3 %) with hypertension stage I, 8 persons (12.3 %) — with hypertension stage II and 49 persons (75.4 %) — with hypertension stage III; 27 females and 38 males. The average age was 53.7 ± 10.1 years. All patients complained of snoring and/or excessive daytime sleepiness. Exclusion criteria were: functional class IV (NYHA) chronic heart failure, cardiac arrhythmias at the time of the study, cerebrovascular accident, myocardial infarction less than 6 months before the study, history of bronchial asthma, anemia, malignant neoplasms, or ENT diseases.

The diagnostic procedures included physical examination and anthropometric measurements. Office blood pressure was measured on the brachial artery three times with a 2–3-minute interval by Korotkoff method. Hypertension was diagnosed according to the National Guideline for the Diagnosis and Treatment of Arterial Hypertension [7]. Hypertension duration was determined based on medical records and past history. All patients received personalized antihypertensive therapy that was discontinued 3 days prior to the HRV test. Captopril was used for symptomatic therapy.

All patients underwent cardiopulmonary monitoring (CPM) and ECG recording with subsequent HRV analysis. CPM was carried out using the device ResMed, ApneaLink (Germany). This device can register respiratory flow and oxygen saturation during sleep. It is used for OSAS screening. The study protocol includes the assessment of the number of apnea or hypopnea episodes, air flow limitation, snoring, blood oxygen saturation, Cheyne–Stokes respiration episodes during the recording.

Apnea-hypopnea index (AHI) measures the number of apnea or hypopnea episodes per hour of recording. Apnea was determined as full air flow cessation lasting more than 10 seconds. Hypopnea is air flow reduction by more than 50 % or restriction by more than 30 % combined with saturation reduction by 3 % or more, lasting more than 10 seconds. The number of apnea episodes per hour of recording is commonly referred to as apnea index (AI), the number of desaturation episodes per hour of recording — desaturation index (DI). Both parameters can be used for the assessment of severity of breathing disorders during sleep.

OSAS was diagnosed according to the recommendations of the American Academy of Sleep

Table 1

GROUP CHARACTERISTICS

Parameter	Mild and moderate OSAS (n = 26)	Severe OSAS (n = 39)	p
BMI, kg/m^2	35.19 ± 7.35	40.15 ± 8.53	0.019
Age, years	52.73 ± 10.9	54.38 ± 8.29	0.490
Males/females, n	13 / 13	25 / 14	0.265
Hypertension duration, years	8.52 ± 6.53	10.59 ± 5.61	0.182
Mean SBP, mm Hg	150.84 ± 21.44	148.77 ± 22.00	0.712
Mean DBP, mm Hg	83.28 ± 12.65	85.41 ± 13.54	0.531
AHI, episodes/hour of sleep	9.28 ± 7.34	54.61 ± 16.9	< 0.001
AI, episodes/hour of sleep	4.20 ± 5.09	37.7 ± 20.5	< 0.001
DI, episodes/hour of sleep	13.23 ± 11.66	49.39 ± 16.5	< 0.001
Mean apnea duration, sec	48.14 ± 9.86	32.3 ± 9.6	< 0.001
Epworth sleepiness scale, score	6.53 ± 3.99	12.76 ± 6.80	0.003

Note: OSAS — obstructive sleep apnea syndrome; BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; AHI — apnea-hypopnea index; AI — apnea index; DI — desaturation index.

Medicine [8]. Daytime sleepiness was measured using the Epworth sleepiness scale [9].

The HRV was assessed using the NeuroSoft system (Russia) and its Poly-Spektr-Rhythm software module. The examination included ECG recording at rest (300 RR intervals) and during an active tilt test. HRV assessment was carried out from 11.00 a.m. to 12.00 p.m. The patients were examined in the fasted state. After the 10-minute rest in supine position ECG in the standard lead I was recorded (300 RR intervals). Then a patient was asked to stand up quickly (orthostatic tilt test). For 6 minutes ECG was recorded in the upright position. Then the spectral analysis of the data was carried out. Spectrum total power (TP) as well as very low frequency (VLF), low frequency (LF) and high frequency (HF) powers were assessed in absolute power units — squared milliseconds (ms2), in relative power units — normalized units (LFnu and HFnu) and in percents. Vagosympathetic balance ratio (LF/HF) was calculated.

The study was approved by the local ethics committee. All patients signed written informed consent.

Statistical analysis was carried out with the use of Statistica 6.0 software. Pearson correlation coefficient (r) was used to assess the relation between studied parameters. To evaluate the significance of differences, Student t-test and Mann–Whitney U-test for independent groups were used. Within-subject comparisons were carried out using the sign test. Data are presented as M ± σ. Difference was considered significant at $p < 0.05$.

Results

Based on the data of all examinations the patients were divided into 2 groups according to their OSAS severity. The first group included 26 subjects with AHI not more than 30 episodes per hour of sleep (mild and moderate OSAS), the second group included 39 subjects with AHI ≥ 30 episodes per hour of sleep (severe OSAS). Group characteristics are presented in Table 1.

All CPM parameters as well as the body mass index in groups 1 and 2 were significantly different. The groups were matched by age, sex and hypertension characteristics.

Correlation analysis of CPM and HRV parameters among all examined subjects showed an association between the increase in humoral-metabolic and sympathetic effects on the heart rate and the increase of OSAS severity.

With the increase of AHI and AI, the proportion of VLF waves in the total spectrum also increased ($r = 0.300$, $p = 0.039$ and $r = 0.391$, $p = 0.010$, respectively). The proportion of these waves decreased as the average duration of the apnea episode decreased ($r = –0.347$, $p = 0.048$). At the

Table 2

CORRELATION BETWEEN THE PARAMETERS OF HEART RATE VARIABILITY AND CARDIOPULMONARY MONITORING AT REST

Parameter	LF/HF		TP mc²		LF nu		HF nu	
	Mild and moderat OSAS	Severe OSAS	Mild and moderat OSAS	Severe OSAS	Mild and moderat OSAS	Severe OSAS	Mild and moderat OSAS	Severe OSAS
AHI, episodes/ hour of sleep	0.153	**0.427***	0.167	**–0.404***	0.171	0.333	–0.171	–0.333
AI, episodes/ hour of sleep	0.029	**0.461***	–0.014	**–0.554***	0.195	**0.461***	–0.195	–0.462*
DI, episodes/ hour of sleep	**0.638***	0.294	0.043	0.039	0.341	0.137	–0.341	–0.137
Minimal saturation, %	**–0.726***	–0.129	0.134	–0.098	–0.325	–0.115	0.325	0.115
Mean apnea duration, sec	–0.452	–0.107	0.344	0.469	–0.347	–0.095	0.347	0.095

Note: LF/HF — ratio LF/HF; TP msec2 — total power spectrum, msec2; LF nu — proportion of LF waves, nu; HF nu — proportion of HF waves, nu; OSAS — obstructive sleep apnea syndrome; AHI — apnea-hypopnea index; AI — apnea index; DI — desaturation index; * — p < 0.05.

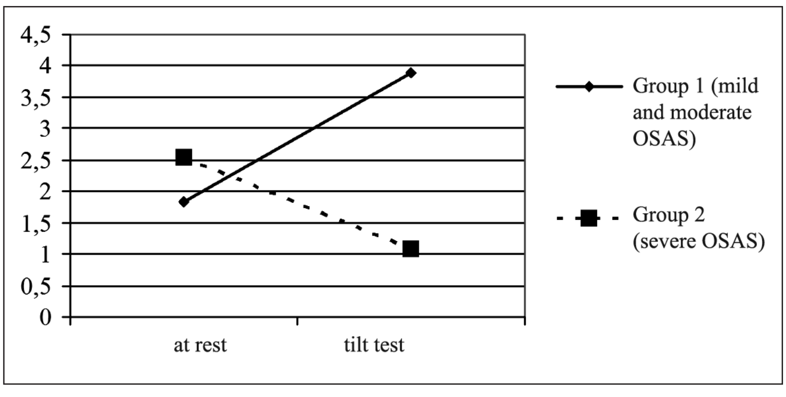
same time, the average duration of apnea decreased simultaneously with the increase of OSAS severity (r = –0.686, p < 0.001).

In the patients with more severe OSAS the CPM showed lower values of the minimal oxygen saturation during the apnea episodes (r = –0.518, p < 0.001). Reductions in blood oxygen levels caused the increase of sympathetic effects on the heart rate — an inverse correlation between the LF/HF ratio and the minimal blood oxygen level during the recording (r = –0.368, p = 0.015) was found.

In group 1, the tendency for the predominance of sympathetic effects in heart rate regulation was observed: with DI increase, the LF/HF ratio also increased. DI directly correlated with AHI (r = 0.911, < 0.001), and that might correspond with the severity of sleep-disordered breathing (Table 2).

No significant correlation with LFnu and HFnu was found in this group but the tendency for the increase of humoral effects persisted. The VLF waves percentage increased considerably with DI increase (r = 0.485, p = 0.026). Inverse correlation was found between

Figure. LF/HF ratio at rest and at tilt test



Note: OSAS — obstructive sleep apnea syndrome.

Table 3

TOTAL POWER SPECTRUM AT REST AND AFTER TILT TEST (INTERGROUP COMPARISON)

Parameter	VLF, %		LF, %		HF, %	
	At rest	Tilt test	At rest	Tilt test	At rest	Tilt test
Mild and moderate OSAS	33.94 ± 19.57	44.70 ± 19.04	30.37 ± 14.92	32.82 ± 13.14	**35.48 ± 20.71**	**22.47 ± 17.62***
Severe OSAS	42.55 ± 28.02	38.77 ± 25.33	23.07 ± 11.62	22.62 ± 7.11	**34.36 ± 26.80**	**38.58 ± 22.01***

Note: VLF, % — proportion of very low frequency waves in the total power spectrum, %; LF, % — proportion of low frequency waves in the total power spectrum, %; HF, % — proportion of high frequency waves in the total power spectrum, %; OSAS — obstructive sleep apnea syndrome; * — $p < 0.05$.

Table 4

HEART RATE VARIABILITY DURING TILT TEST IN STUDIED GROUPS (BETWEEN-GROUP COMPARISON)

Parameter	Mild and moderate OSAS	Severe OSAS	p
LF nu	66,67 ± 22,65	39,94 ± 16	**0,001**
HF nu	33,34 ± 22,64	60,06 ± 16	**0,001**
LF/HF	3,89 ± 4,15	1,07 ± 1,57	**0,002**

Note: OSAS — obstructive sleep apnea syndrome; LF nu — proportion of LF waves, nu; HF nu — proportion of HF waves, nu; LF/HF — LF/HF ratio.

the relative VLF value and minimal saturation ($r = -0.506$, $p = 0.019$) as well as between the relative VLF value and average apnea episode duration ($r = -0.584$, $p = 0.017$). Therefore, in this group a significant impact of VLF waves on the heart rate regulation was found, which gives evidence of the regulation shift to the suprasegmental humoral-metabolic level.

Main CPM parameters (AHI, AI) in this group do not correlate with HRV values, possibly due to mild and moderate cardiopulmonary disorders during sleep.

In group 2 the severity of breathing disorders was directly related to the heart rate: as AHI and AI increased, the proportion of LF waves and LF/HF ratio also increased whereas HF waves decreased proportionally (Table 2).

As for the impact of VLF waves on heart rate regulation, in this group the increase of the proportion of humoral-metabolic effects corresponded to the OSAS severity (for AHI — $r = 0.472$, $p = 0.017$; for AI — $r = 0.602$, $p = 0.003$). Triggered activity with regard to the cardiovascular autonomic regulation seems to be specific only for severe OSAS.

During the tilt test in group 1 the total spectrum power increased due to higher contribution of low frequency and very low frequency waves. The proportion of HF waves in absolute power units decreased (Table 3). LF/HF ratio during the tilt test increased (Image 1). Therefore, there is evidence of excessive sympathetic activation of heart rate regulation and regulation shift to the suprasegmental humoral level in hypertensive patients with AHI less than 30 episodes per hour of sleep.

In group 2 the spectrum total power during the tilt test increased several-fold. Paradoxical increase of the proportion of high frequency waves (HF) in the heart rate regulation was noted (Table 3). LF/HF ratio decreased (Figure). Percentage distribution of the waves was nearly normal, although the sympathetic activity was excessive. Increased proportion of very low frequency waves in the total spectrum indicates excessive humoral-metabolic effects on the heart rate during the functional test.

Different reactivity of the autonomic nervous system in response to the load in patients with various severity of OSAS is evidenced by the data obtained by between-subject analysis using the Mann-Whitney U-test for independent groups (Table 4). These data support the opposite effect of the branches of the autonomic nervous system on HRV during the tilt test in two groups.

Discussion

Findings of the studies concerned with HRV assessment in OSAS are inconsistent. First of all, they differ in their methodological approach. ECG recordings of different length are analyzed, both temporal and spectral parameters are used for analysis.

HRV is usually assessed based on 24-hour Holter ECG monitoring or night ECG recordings obtained during polysomnography.

The majority of studies showed the decrease of the proportion of HF waves and increase of LF/HF ratio in patients with OSAS compared to patients without sleep-disordered breathing as well as in case of the increase of OSAS severity [10, 11].

Our analysis showed no difference between groups 1 and 2 at rest with regard to LF, HF, VLF, and LF/HF ratio. However, the tendency for the increase of the proportion of LF waves, decrease of the platelet count and the proportion of HF waves in the total spectrum was observed with the increase in AHI. Previous studies showed similar results [10, 11].

A number of authors also noted the increase of VLF and HF waves proportion in the total spectrum [12, 13], which was considered to be due to the apparent sleep-related respiratory arrhythmia in patients with OSAS. We assume that such changes in heart rate regulation persist during waking hours.

V. M. Mikhailov et all studied the reactivity of the autonomic nervous system in hypertensive patients. According to his findings, hypertensive patients with left ventricular hypertrophy, during the tilt test showed an increase in the activity of humoral-metabolic effects on the heart rate (increase of VLF waves proportion). At the same time the response of the sympathetic system was weaker. Our results in the group of patients with mild and moderate OSAS were consistent with these data. In these patients the effect of OSAS on HRV might be less significant than the impact of hypertension.

In the study by L. T. Montemurro et all (2014) differences in the VLF component in patients with severe OSAS were found to depend on the severity of daytime sleepiness. The authors consider the VLF component as a marker of sympathetic impact on HRV, together with the LF component [14]. The authors suggest that the absence of daytime sleepiness in some patients with severe OSAS is explained by the high sympathetic activity manifested by high VLF values in this group compared to the patients with complaints of daytime sleepiness. In our study the increase of VLF waves proportion in the total power spectrum was also found in both groups.

The present study has a number of limitations. HRV values obtained during the recording of short periods in the daytime are not always well reproducible. Moreover, high variability is found in the group of patients with originally normal ECG and without any cardiovascular diseases. The highest value range might be found in the VLF spectrum (ms2). Therefore, the analysis of the VLF component in the heart rate regulation using the short recordings should only be conducted with regard to the clinical data, and assumptions about the possible genesis of these waves should also be made with certain caution. At the same time spectral analysis on the basis of Fourier transformation analysis and assessment of the body reactivity during the functional tests are as good as impossible in a 24-hour recording [15].

Conclusions

1. Patients with hypertension combined with OSAS demonstrate autonomic imbalance with sympathetic hyperactivity based on the analysis of short ECG recordings at rest and during the tilt test at daytime.

2. With the increase in OSAS severity in hypertensive patients, excessive sympathetic activation takes place which is manifested in the increase of VLF and LF waves proportions in the heart rate.

3. In patients with hypertension the tilt test shows oppositely directed innervation depending on OSAS severity. In the group with mild and moderate OSAS, excessive sympathetic regulation of the heart rate is found. In the group with severe OSAS, parasympathetic regulation prevails.

Conflict of interest

The authors declare no conflict of interest.

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Author information:

Vladimir V. Shchekotov, MD, PhD, Professor, the Chief of the Department of Internal Medicine with the Policlinic Course at Perm State Medical University named after academic E.A. Vagner;

Pavel N. Barlamov, MD, Professor of the Department of Internal Medicine with the Policlinic Course at Perm State Medical University named after academic E.A. Vagner;

Ekaterina A. Luchnikova, Post-Graduate of the Department of Internal Medicine with the Policlinic Course at Perm State Medical University named after academic E.A. Vagner.