O. I. Tokarenko, Ia. O. Andreieva
State Institution «Zaporizhzhia Medical Academy of post-graduate education Ministry of Health of Ukraine»
Zaporizhzhia, Ukraine

O. I. Токаренко, Я. О. Андреєва
Державний заклад «Запорізька медична академія післядипломної освіти Міністерства охорони здоров'я України»
Запоріжжя, Україна

HEART RATE VARIABILITY IN PATIENTS WITH OBSTRUCTIVE SLEEP APNOEA SYNDROME

Варібельність серцевого ритму при синдромі обструктивного апное сну

Abstract

Purpose of the study. *To assess 24-hours heart rate variability in patients with obstructive sleep apnea syndrome*

Materials and Methods. *The 143 eligible patients with OSA were enrolled into the main group in this study. Twenty healthy subjects with increased body weight and without significant chronic pathologies were included into the control group. The mean age and gender characteristics of the groups were similar. Each patient underwent a clinical evaluation during the consultation (with measurement of body mass, height, circumference of the neck, waist and hips), biological tests, cardio-respiratory monitoring and Holter ECG monitoring.*

Results and discussion. *The average daily HR, HR_{max} and HR_{min} the main group was higher in comparison with the control group, but these changes had no significant differences ($p \geq 0,05$). The heart rate analysis at night in patients with OSAS revealed the presence of periodic episodes of severe bradycardia (up to 28 beats/min) with subsequent episodes of tachycardia and normalization of heart rhythm. Episodes of bradycardia/tachycardia during sleep in patients with OSAS could be explaned as the response of the autonomic nervous system to periods of apnea/hypopnea. It was found that most indicators in patients of the main group and control group differed statistically significant in the HRV analysis. Thus, SDNN and RMSSD in patients from main group were lower than the corresponding values in the control group ($p = 0,022$, $p = 0,038$, respectively). During the day the value of pNN50 did not differ significantly between the groups, but at night this parameter decreased but was lower*

Реферат

Мета дослідження. *Оцінити варіабельність серцевого ритму протягом доби у пацієнтів з синдромом обструктивного апное сну.*

Матеріали та методи. *Обстежено 143 пацієнти з синдромом обструктивного апное сну (основна група). Контрольну груп склали 20 осіб. Усім учасникам дослідження проведено загально-клінічне обстеження з обов'язковим вимірюванням окружності шиї, талії та стегон, кардіо-респіраторний та добовий моніторинг ЕКГ.*

Результати та обговорення. *Більшість показників варіабельності серцевого ритму у пацієнтів основної групи мають статистично достовірну різницю у порівнянні з показниками контрольної групи. SDNN та RMSSD були достовірно нижче ніж відповідні показники у контрольній групі ($p \geq 0,05$). Спостерігалось патологічне збільшення спектральних показників VLF, LF, LFN як у денний, так і у нічний час. Потужність спектрів високих частот у основній групі була нижча, не фіксувалось достатнього підйому HF та HFN у нічний час на відміну від контрольної групи.*

Висновки. *При СОАС встановлено дисбаланс ланок автономної вегетативної системи, що проявлявся в патологічному підвищенні активності симпатичного відділу вегетативної нервової системи як у день, так і в ночі. Встановлено прямий та зворотний кореляційний зв'язок індексу апное-гіпопное з індексом маси тіла ($r = 0,73$, $p < 0,05$), окружністю шиї ($r = 0,71$, $p < 0,05$), та показниками $SDNN_{night}$ ($r = -0,71$, $p < 0,05$), LF_{night} ($r = 0,70$, $p < 0,05$), $RMSSD_{night}$ ($r = -0,63$, $p < 0,05$).*

by 40% from the control value ($p = 0,007$). The maximum values during the day for SDNN and pNN50 in the main group were resisted at night in comparison with the control group. There was a pathological increase in the spectral parameters (VLF, LF, LFN) during the day and at night in patients with OSAS, which indicated persistent hypersympathicotonia during daytime and nighttime. During the correlation analysis, a direct correlation was established between AHI, BMI and neck circumference ($r = 0,73$, $p = 0,007$; $r = 0,71$, $p=0,003$, respectively). When compared with the spectral indices of HRV, an inverse correlation was established between the indices $SDNN_{night}$, and AHI ($r = -0,71$, $p = 0,024$), a positive correlation between LF_{night} and AHI ($r = 0,70$, $p = 0,011$) and the negative correlation between AHI and RMSSDnight ($r = -0,63$, $p = 0,013$).

Conclusions. It was shown that all patients with OSAS have Imbalance between branches of the automatic nervous system which manifest as an pathological increase of activity of sympathetic branch in the day, and at night as well. A significant correlations between AHI and BMI ($r = 0,73$, $p = 0,007$), neck circumference ($r = 0,71$, $p = 0,003$), and $SDNN_{night}$ ($r = -0,71$, $p = 0,024$), LF_{night} ($r = 0,70$, $p = 0,011$), $RMSSD_{night}$ ($r = -0,63$, $p = 0,013$)) were established.

Keywords: heart rate variability, obstructive sleep apnoea syndrome, obesity.

Ключові слова: варіабельність серцевого ритму, синдром обструктивного апное сну, ожиріння.

Obstructive sleep apnea syndrome (OSAS) is defined as a pathological condition in which the patient has repeated, short-term asphyxia due to complete or partial narrowing of the airways during sleep, accompanied by sound snoring, oxygen desaturation and frequent awakenings [1].

The prevalence of OSAS, according to various authors, ranges from 1,7 to 28,0% in the general population. The highest prevalence of OSAS among obese people is 18−52%, patients with cardiac pathologies (hypertension, coronary artery disease, heart failure) − 20−40%, the elderly (over 60 years) − 26−73%. It is believed that men are more often to suffer from OSAS than women (ratio 3−5 to 1 in the general population) [2].

At the same time, patients with OSAS suffer from poor sleep quality, increased daytime sleepiness, frequent depression, low quality of life, have an increased risk of accidents. Numerous studies have shown that OSAS is associated with an increased risk of developing and progressing of cardiovascular diseases, obesity, diabetes, etc. The most common complication during apnoea episodes is arrhythmias and sudden cardiac death associated with them [3]. A. Tilkian et al. was one of the first to report an association between OSAS and cardiac arrhythmias at 1976. Ventricular arrhythmias and ventricular tachycardia were found in 67% of the patients with OSAS examined by them. Subsequently, more than 300 studies have been conducted to study the relationship between OSAS and arrhythmias, but their results still remain controversial [4]. Many authors only support the point of view that the most common type of arrhythmia in such patients is cyclic fluctuations in heart rate with frequent episodes of bradycardia during apnoea and normalisation of the heart rate after restoration of breathing. Such episodes of sinus arrhythmia are registered in more than 75% of patients. The degree of bradycardia correlates with the degree of oxygen desaturation during apnoea episodes. These changes driven by changes autonomic nervous system activation, but data of studies about the stages of activation are also contradictory.

It is possible to characterise the state of different branches the autonomic nervous system in physiological and pathological conditions by investigation of different parameters of heart rate variability (HRV). At the present hour, it has been reported that HRV has a high predictive value, given the simplicity of the preliminaries.

PURPOSE OF THE STUDY

The aim of the study was to assess 24-hours heart rate variability in patients with obstructive sleep apnea syndrome.

MATERIALS AND METHODS

The observational study was conducted in the therapeutical and pulmonogical departments of the CU "Central hospital of Komunarskyi district" and CU "City hospital №1" from May, 2017 to June, 2021.

The 143 eligible patients with OSA were enrolled into the main group in this study. Twenty healthy subjects with increased body weight and without significant chronic pathologies were included into the control group. The mean age and gender characteristics of the groups were similar.

The research was approved by the clinical research ethics committee of SI "Zaporizhzhia Medical Academy of Post-Graduate Education Ministry of Health of Ukraine". Written informed consent was obtained from all patients. This research was conducted in accordance with "the 1964 Helsinki Declaration."

Exclusion criteria from the study were the following: rejection to sign the informed consents, patients with known cardiovascular pathologies, respiratory pathologies, diabetes or thyroid dysfunction, any known renal diseases, cognitive impairment, dementia, drug and alcohol abuse, skin diseases.

Each patient underwent a clinical evaluation during the consultation (with measurement of body mass, height, circumference of the neck, waist and hips), biological tests, cardio-respiratory monitoring and Holter ECG monitoring. The values of BMI, waist and hips circumferences did not differ significantly between both groups (Table 1).

Table 1

Clinical characteristics of the examined persons

Показник	Main group (n = 143)	Control group (n = 20)	p-value
Age, years	$49,7 \pm 7,6$	$47,6 \pm 6,9$	p = 0,362
Man/women	80/63	11/9	-
BMI, kg·m^2	$31,4 \pm 1,5$	$28,4 \pm 2,2$	p = 0,166
The waist Circumference, cm	$92,5 \pm 2,3$	$94,6 \pm 3,2$	p = 0,185
The neck circumference, cm	$36,4 \pm 1,6$	$32,3 \pm 1,2$	p = 0,106
The hip circumference, cm	$93,6 \pm 5,3$	$96,4 \pm 2,5$	p = 0,093
AHI, events per hour	$22,4 \pm 2,8$	$1,8 \pm 0,6$	p = 0,001

Cardio respiratory monitoring was conducted for OSAS diagnosis by Somno check 2.0 (Weinmann, Germany). The apnea-hypopnea index (AHI) was de fine das the number of apneas and hypopneas per hour of sleep. According to the recommendations of the American Academy of Sleep Medicine (ICSD-3, 2014), OSAS was diagnosed with an apnea-hypopnea index (AHI) of more than 5 [5]. Desaturation index (DI) was defined as the percentage of sleep time with oxygen saturation < 90 %.

Interpretation of heart rate variability (HRV) were performed in accordance with the recommendations of the European Society of Cardiology. Holter ECG was performed on the CardioSense (KHAI-Medica, Ukraine). The program automatically calculated the mean heart rate per day (HRmean), minimum heart rate per day (HRmin) and maximum heart rate per day (HRmax), absolute power of the very-low-frequency band (VLF), peak frequency of the low-frequency band (LF) and peak frequency of the high-frequency band (HF), expressed as in absolute and normalized units (LFN, HFN), their ratio (LF/HF), as well as the total power of the spectrum (TP), the standard deviation of RR intervals (SDRR), percentage of successive RR intervals that differ by more than 50 ms (NN50), root mean square of successive RR interval differences (RMSSD), the average duration of the RR intervals (mRR).

Statistical analysis. The quantitative variables were expressed as means ± SD. Categorical variables were presented as percentages. The differences in each variable were evaluated by the Student's t-test for continuous variables and the χ^2 test for categorical variables. The relationships between parameters were evaluated by Pearson correlation analysis. A P-value < 0,05 was considered as an indication statistically significant difference between groups. Calculations were performed with SPSS-software (Version 23.0; SPSS, Chicago, IL).

RESULTS AND DISCUSSION

The average daily HR, HRmax and HRmin the main group was higher in comparison with the control group, but these changes had no significant differences (p ≥ 0,05). The heart rate analysis at night in patients with OSAS revealed the presence of periodic episodes of severe bradycardia (up to 28 beats/min.) with subsequent episodes of tachycardia and normalization of heart rhythm. Episodes of bradycardia/tachycardia during sleep in patients with OSAS could beexplaned as

the response of the autonomic nervous system to periods of apnea/hypopnea.

It was found that most indicators in patients of the main group and control group differed statistically significant in the HRV analysis. Thus, SDNN and RMSSD in patients from main group were lower than the corresponding values in the control group (p = 0,022, p = 0,038, respectively). During the day the value of pNN50 did not differ significantly between the groups, but at night this parameter decreased but was lower by 40% from the control value (p = 0,007). The maximum values during the day for SDNN and pNN50 in the main group were resisted at night in comparison with the control group. There was a pathological increase in the spectral parameters (VLF, LF, LFN) during the day and at night in patients with OSAS, which indicated persistent hypersympathicotonia during daytime and nighttime. At the same time, the sufficient decrease in spectral indices (VLF, LF, LFN) at night did not occur in the main group in comparison with HRV standards and changes in main group (p = 0,104; p = 0,447; p = 0,187). The power of the high frequency spectra in the main group was lower relative to the control groups. Also, in OSAS, a Asufficient rise in HF and HFN was not recorded at night, in contrast to the control group (Table 2).

Table 2

Parameters of heart rate variability in studied groups

	Main group (n = 143)		Control group (n = 20)		p-value	
	Day	Night	Day	Night	p_1	p_2
HR, beats/min	84,1 ± 8,9	70,4 ± 14,2	78,8 ± 12,1	53,8 ± 10,5	0,091	0,012
HR_{Max}, beats/min	123,8 ± 10,6	79,3 ± 14,2	96,2 ± 15,2	66,3 ± 4,9	0,174	0,088
HR_{min}, beats/min	64,4 ± 12,6	56,2 ± 11,3	56,7 ± 9,1	49,4 ± 10,6	0,255	0,033
mRR (мsec)	988,4 ± 81,4	823,2 ± 79,3	659,3 ± 78,4	615,4 ± 68,6	0,003	0,137
SDNN (мsec)	31,5 ± 11,7	44,2 ± 11,4	52,3 ± 13,4	45,2 ± 12,4	0,016	0,096
RMSSD (мsec)	31,8 ± 9,6	37,2 ± 14,6	43,5 ± 11,5	41,4 ± 13,3	0,007	0,021
pNN50 (%)	6,8 ± 3,2	9,2 ± 4,8	9,6 ± 3,9	16,7 ± 7,1	0,288	0,013
VLF (мsec²)	1977,5 ± 451,7	1810,1 ± 318,2	711,3 ± 316,3	1243,2 ± 311,8	0,005	0,003
LF (мsec²)	543,8 ± 52,4	468,2 ± 70,2	415,2 ± 61,2	313,2 ± 59,8	0,031	0,022
LFN (%)	74,1 ± 8,4	67,3 ± 9,1	49,2 ± 7,2	38,4 ± 8,2	0,018	0,007
HF (мsec²)	88,1 ± 14,2	131,4 ± 13,5	228,7 ± 28,7	314,2 ± 28,4	0,001	0,005
HFN(%)	31,6 ± 6,2	38,3 ± 8,4	23,8 ± 7,4	36,4 ± 7,2	0,022	0,158
LF/HF	1 : 5	1 : 4	1 : 2	1 : 1	-	-
TP (мsec²)	1121,7 ± 134,6	2018,2 ±145,1	1378,6 ± 113,6	956,7 ± 128,6	0,287	0,002

During the correlation analysis, a direct correlation was established between AHI, BMI and neck circumference (r = 0,73, p = 0,007; r = 0,71, p = 0,003, respectively). When compared with the spectral indices of HRV, an inverse correlation was established between the indices SDNNnight, and AHI (r = −0,71, p = 0,024), a positive correlation between LFnight and AHI (r = 0,70, p = 0,011) and the negative correlation between AHI and RMSSDnight (r = −0,63, p = 0,013).

The results of the analysis of indicators of HRV in OSAS indicate the presence of severe autonomic imbalance, manifested by increased activity of the sympathetic nervous system both during the day and night and, accordingly, a pathological decrease in activity of the parasympathetic autonomic nervous system.

Our data are explained by the fact that obstruction of the upper respiratory tract during sleep and the resulting hypoxia is a powerful irritant to the nervous system. Intermittent hypoxia and recurrent sympathicotonia during the night, irritation of chemo- and baroreceptors, hyperproduction of catecholamines, endothelial dysfunction and hemodynamic reactions can lead to a shift in autonomic balance not only at night but also during the day. All this leads to the modification of the adrenergic systems of the body [6, 7]. This primarily applies to changes in the sensitivity of peripheral adrenergic receptors. Thus, in several experiments it has been shown that there is a decrease in the sensitivity of β_2-adrenergic receptors in patients with OSAS [6, 8]. In addition, an increase in serum norepinephrine concentrations has been reported in patients with OSAS [6, 8]. This may be one of the reasons for the decrease in HRV during the day in OSAS. Further differentiated determination of HRV changes at different degrees of severity of OSAS, as well as dynamic study of HRV on the background of OSAS

therapy will complement the already established pathogenetic mechanisms of development and progression of the disease and its complications.

CONCLUSIONS

1. It was shown that all patients with OSAS have Imbalance between branches of the automatic nervous system which manifest as an pathological increase of activity of sympathetic branch in the day, and at night as well.

2. A significant correlations between AHI and BMI ($r = 0,73$, $p = 0,007$), neck circumference ($r = 0,71$, $p = 0,003$), and $SDNN_{night}$ ($r = -0,71$, $p = 0,024$), LF_{night} ($r = 0,70$, $p = 0,011$), $RMSSD_{night}$ ($r = -0,63$, $p = 0,013$)) were established.

REFERENCE

1. Jordan A, Mc Sharry D, Malhotra A. Adult obstructive sleep apnoea. The Lancet. 2014; 383: 736–747.

2. Aeschbacher S, Bossard M, Schoen T. et al. Heart Rate Variability and Sleep-Related Breathing Disorders in the General Population. Am. J. Cardiol. 2016; 118 (6): 912–917.

3. Xuehao G, Leidan H, Xin L. Correlation Analysis between Polysomnography Diagnostic Indices and Heart Rate Variability Parameters among Patients with Obstructive Sleep Apnea Hypopnea Syndrome. PLoS One. 2016: 11. https://doi.org/10.1371/journal.pone.0156628.

4. May AM, Van Wagoner DR, Mehra R. Obstructive Sleep Apnea and Cardiac Arrhythmogenesis: Mechanistic Insights. Chest. 2017: 151 (1); 225–241. DOI: 10.1016/j.chest.2016.09.014.

5. Mansukhani M, Kolla B, Ramar K. International Classification of Sleep Disorders 2 and American Academy of Sleep Medicine Practice Parameters for Central Sleep Apnea. Mansukhani M. Sleep Medicine Clinics.2014; 9 (1): 1–11.

6. Chouchou F, Pichot V, Barthelemy J-C. et al. Cardiac Sympathetic Modulation in Response to Apneas/Hypopneas through Heart Rate Variability Analysis. PLoSOne. 2014; 9. https://doi.org/10.1371/journal.pone.0086434.

7. Alvarez-Estevez D, Moret-Bonillo V. Spectral Heart Rate Variability analysis using the heart timing signal for the screening of the Sleep Apnea-Hypopnea Syndrome. Comput. Biol. Med. 2016; 71: 14–23.

8. Eichhorn L, Erdfelder F, Kessler F. Influence of Apnea-induced Hypoxia on Catecholamine Release and Cardiovascular Dynamics. Int. J. Sports Med. 2016; 7. doi: 10.3791/54933.