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Effects of obstructive sleep apnea on cardiac autonomic nervous homeostasis

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ABSTRACT

Objective: To investigate the effect of obstructive sleep apnea hypopnea syndrome (OSAHS) on cardiac autonomic nervous homeostasis. Methods the patients with OSAHS diagnosed in our hospital were the observation group, and the non OSAHS patients in the same period were the control group. The differences of baseline data, sleep monitoring, time domain analysis index of heart rate variability, peripheral blood methoxyepinephrine (MN) and methoxynorepinephrine (NMN) between the two groups were analyzed. The observation group was divided into light, medium and heavy groups according to apnea index (AHI), and the correlation analysis between age, AHI, lsao2, time domain index and blood catecholamine metabolites was carried out. **Results:** Ahi was negatively correlated with SDNN and PNN50% ($P < 0.01$) and positively correlated with NMN ($p < 0.05$); lsao2 was positively correlated with SDNN and PNN50% ($P < 0.05$), and negatively correlated with vanillic acid 2 ($p < 0.05$). Conclusion patients with OSAHS have obvious disturbance of cardiac sympathetic and vagus nerve balance at night.

Keywords: cardiology; obstructive sleep apnea syndrome; heart rate variability: blood catecholamine; relevance

Obstructive sleep apnea hypopnea syndrome (OSAHS) is a kind of apnea and hypopnea caused by upper respiratory tract obstruction during sleep. OSAHS pathological respiration will disturb the respiratory activity of patients during normal sleep, and cause pathological changes such as decreased arterial oxygen saturation (sao_2) and hypercapnia. Studies have shown that OSAHS has a significant correlation with cardiovascular diseases. It is considered to be an independent controllable risk factor for cardiovascular diseases such as arrhythmia and coronary heart disease[1]. The balance of sympathetic and parasympathetic interactions in the cardiac autonomic nerve maintains the normal electrical activity of the heart. Once the balance of the two is destroyed, various electrical activity abnormalities, arrhythmias and even sudden death will occur. Heart rate variability (HRV) is a noninvasive method to evaluate the cardiac autonomic nerve regulation function. The detection of catecholamine in peripheral blood in the morning can reflect the sympathetic nerve activity at night. The author mainly analyzed the data of sleep monitoring, HRV and the concentration of catecholamine (CA) in peripheral blood of OSAHS patients in our hospital to evaluate the cardiac autonomic nervous activity of OSAHS patients, in order to understand the changes of the above data and related factors in OSAHS patients.

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1. Data and methods

1.1. Research object

The study was approved by the ethics committee of the people's Hospital of Xinjiang Uygur Autonomous Region. All patients involved in the investigation were informed and signed the consent form. The study included the observation group of patients who were diagnosed with OSAHS due to sleep snoring in our hospital from January to December 2018, and the control group of patients who had snoring symptoms and failed to meet the OSAHS standard after PSG examination.

1.2. Inclusion and exclusion criteria

OSAHS diagnostic criteria

It complies with the guidelines for the diagnosis and treatment of obstructive sleep apnea hypopnea syndrome (2011 Revision) formulated by the sleep disordered breathing group of the respiratory branch of the Chinese Medical Association[2]: Apneahypneandex (AHI) during 7h sleep every night ≥ 5 times / hour (AHI: The sum of the average number of apnea and hypopnea per hour), accompanied by snoring, daytime sleepiness and other symptoms. According to AHI, OSAHS is divided into mild (5 ≤ AHI ≤ 15), moderate (15 < AHI ≤ 30) and severe (AHI > 30).

Exclusion criteria

Patients with central or complex SAHS were excluded; except for taking digitalis, congenital heart disease and other cardiovascular diseases; exclude patients with cerebrovascular disease, Parkinson's disease, severe organ dysfunction or failure, except chronic obstructive pulmonary disease, metabolic poisoning, water electrolyte disorder, and oral central stimulant and inhibitory drugs; except for endocrine diseases such as thyroid function, abnormal adenohypophyseal function and primary aldosteronism.

1.3. Research methods

Baseline data

The gender, age, neck circumference, abdominal circumference, body mass index (BMI) and other data of the two groups were statistically analyzed.

PSG indicators

Polysomnography monitoring: The subjects were monitored by the Australian PSG compumedicse series for continuous sleep at night for 7h, and then analyzed. Drinking, hypnotics, sedatives and caffeine were prohibited on the day of inspection. The monitoring results are interpreted, analyzed and verified by professional doctors. The analysis data include: AHI, nighttime mean oxygen saturation ($msao_2$,%), nighttime minimum oxygen saturation (($lsao_2$,%), nighttime average heart rate, nighttime fastest heart rate.

HRV.

Medexmaecg-200 ambulatory electrocardiograph and analysis system were used for ambulatory electrocardiograph monitoring and data analysis in all included cases. The duration of data recording was at least 22h. The time domain indicators of HRV were obtained: The overall standard deviation of normal sinus RR interval (SDNN), the root mean square difference of normal continuous sinus RR interval (RMSSD), and the percentage of adjacent RR interval difference > 50ms in the total number of intervals (PNN50%).

Detection of CA metabolites in morning blood

On the morning of the second day after completing the PSG examination, 5 ml of peripheral blood samples were taken, and the blood methoxyepinephrine (Mn, ng/l), methoxynorepinephrine (NMN, ng/l), VMA_1 (vanillic mandelic acid 1, ng/24hr), VMA_2 (vanillic mandelic acid 2, ng/24hr) were detected by liquid chromatography tandem mass spectrometry (LCMS), Epinephrine and norepinephrine produce intermediate metabolites Mn and NMN mainly through the action of catechol methyltransferase and monoamine oxidase in vivo. The final metabolite is vanilla almond, and Mn and NMN have good stability.

1.4. Statistical methods

In this study, spss20.0 statistical software was used for data processing. Single sample kolmorow smironov test is used for normality of measurement data, Levene test is used for homogeneity of variance, and $p > 0.05$ indicates normality and homogeneity of variance of sample data; if the measurement data meet the conditions, the data between the observation group and the control group are compared by two independent sample t-test, and the three groups in the observation group are compared by one-way analysis of variance LSD test. The results are expressed in $\bar{x} \pm s$, $p<0.05$ shows that the difference is statistically significant.

The rank sum test of nonparametric test was performed on the measurement data that did not meet the requirements. Mann Whitney (wilcoxon-w) test was used between two independent samples, Kruskal wallish test was used between multiple groups of samples, and k-w-h single factor pairwise comparison was performed between multiple groups. The data results were expressed in the median (minimum, maximum) [M(min, max)], $p < 0.05$, indicating that the difference was statistically significant; the counting data were expressed as [number of cases, rate (n,%)] and compared between groups χ^2 inspection. Pearson correlation (bivariate correlation) was used for correlation analysis.

2. Results

2.1. Baseline characteristic comparison

Control group 73 cases; there were 193 cases in the observation group, including 47 mild cases, 72 moderate cases and 74 severe cases. There were differences in gender, age, neck circumference, abdominal circumference and BMI between the two groups ($P < 0.01$). See **Table 1**.

Table 1. Baseline data of patients in each group

Group	N	Male / case	Age / year	Neck circumference /cm	Abdominal circumference /cm	BMI
Control group	73	37(50.7)	47(16,70)	38.0±3.7	93.3±9.7	25.3(18.4,33.7)
Observation group	193	140(72.5)*	50(23,82)*	40.8±4.4*	102.5±11.8*	28.3(18.5,40.8)*
Light	47	29(61.7)	51(29,75)	39.0±3.7	98.2±10.4	27.1(20.3,32.9)
Moderate	72	50(69.4)	50(23,77)	40.6±4.4	103.0±10.0△	27.5(22.3,40.5)
Severe	74	61(82.4)	49(26,82)	42.3±4.3△#	104.8±13.5△	28.9(18.5,40.8)△

Note: BMI= body mass index, compared with the control group, *$p < 0.05$; △ $p < 0.05$ In the observation group compared with the mild group, and compared with the moderate group, # $p < 0.05$.

2.2. PSG and HRV data comparison

The $MSao_2$, $LSao_2$, RMSSD and PNN50% in the observation group at night were significantly lower than those in the control group (all $P < 0.01$), and the AHI and the fastest heart rate at night were significantly higher than those in the control group (all $P < 0.01$); there was no difference in mean heart rate and SDNN at night between the two groups. In the observation group, the night $msao_2$ and lsao2 in the severe group were significantly lower than those in the mild and moderate group ($p < 0.05$), and the AHI was significantly higher than those in the mild and moderate group ($p < 0.05$); the PNN50% in the severe and moderate groups was significantly lower than that in the mild group ($p < 0.05$); however, the light, medium and heavy groups had no difference in the fastest heart rate, SDNN and RMSSD at night, as shown in **Table 2 and 3**.

Table 2. Comparison of PSG in each group at night.

Group	*n*	AHI	$MSao_2$/%	$LSao_2$/%	Average heart rate (times / min)	/Maximum heart rate / (times / min)
Control group	73	2.7(0.1,4.9)	94(87,97)	88(75,93)	64.2±9.3	81(59,127)
Observation group	193	25.3(5.0,135.4)*	92(73,95)*	79(21,90)*	65.0±8.6	88(59,240)*
Light	47	8.6(5.0,14.8)	93(90,95)	84(73,90)	61.5±7.5	85(59,124)
Moderate	72	23.2(15.2,29.5)△	92(86,95)△	78(21,87)△	65.9±7.9△	90(66,136)
Severe	74	44.2(30.3,135.4)△#	91(73,95)△	73(37,86)△#	66.4±9.5△	88(59,240)

Note: Compared with the control group, *$p < 0.05$; within the observation group, compared with the mild group, △$p < 0.05$, compared with the moderate group, #$p < 0.05$.

Table 3. Comparison of HRV time domain indexes of patients in each group.

Group	*n*	SDNN/ms	rMSSD/ms	pNN50%/ms
Control group	73	123.0(63.5,179.1)	29.0(10.5,72.5)	8.0(0.3,36.0)
Observation group	193	117.0(57.2,202.0)	27.0(12.2,83.5)*	4.7(0.13,31.2)*
Light	47	119.1(89.4,200.3)	26.8(13.3,61.5)	6.8(0.13,31.2)
Moderate	72	116.5(78.6,194.0)	27.1(13.6,83.5)	5.5(0.22,26.5)△
Severe	74	117.0(57.2,202.0)	26.5(12.2,80.6)	3.1(0.15,28.6)△#

Note: Compared with the control group, *$p < 0.05$; within th $p < 0.05$, compared with the moderate group, #$p < 0.05$.

2.3. CA metabolite comparison

The levels of blood Mn, NMN and VMA_2 in the observation group were significantly higher than those in the control group ($P < 0.05$), and there was no difference in blood VMA_1 between the two groups. Compared with light, medium and heavy groups in the observation group, Mn levels in the moderate and severe groups were significantly higher than those in the mild group ($p < 0.05$); nmn level in severe group was significantly higher than that in mild and moderate group ($p < 0.05$); there is no difference in VMA_1 and VMA_2 among OSAHS patients with different severity, as shown in **Table 4.**

Table 4. Blood catecholamine data of patients in each group.

Group	MN/(ng/L)	NMN/(ng/L)	VMA_1/(ng/24hr)	VMA_2/(ng/24hr)
Control group	21.4(12.3,62.2)	74.4±47.3	5.3(3.9,10.5)	6.3(4.0,10.5)
Observation group	41.3(8.5,75.5)*	95.3±54.4*	6.3(3.7,10.2)	8.1(3.9,10.2)*
Light	23.4(8.5,60.2)	80.5±40.6	6.3(4.0,9.6)	6.8(3.9,9.8)
Moderate	41.4(10.5,64.8)△	91.8±52.2	5.5(4.1,10.2)	8.1(3.9,10.2)
Severe	43.2(10.2,75.5)△	109.8±58.3△#	6.3(3.7,9.7)	8.2(4.1,9.9)

Note: Compared with the control group, *p < 0.05; within the observation group, compared with the mild group, △p < 0.05, compared with the moderate group, \p < 0.05.

2.4. Correlation analysis

The age of OSAHS patients was negatively correlated with SDNN, RMSSD, PNN50%, and the age of patients was positively correlated with blood NMN; ahi was negatively correlated with SDNN, PNN50% and positively correlated with blood NMN in OSAHS patients; $lsao_2$ was positively correlated with SDNN and PNN50% and negatively correlated with VMA_2 in OSAHS patients, **Table 5**.

Table 5. Correlation Analysis between HRV, CA metabolites and other indicators in patients with oasha.

Index	Age		AHI		$LSaO_2$	
	R	***P***	***R***	***P***	***R***	***P***
SDNN	–0.16	0.02	–0.24	0.001	0.21	0.003
rMSSD	–0.19	0.009	–0.05	0.47	0.01	0.91
pNN50%	–0.20	0.007	–0.31	<0.001	0.15	0.03
MN	0.06	0.39	0.03	0.65	–0.05	0.53
NMN	0.11	0.04	0.14	0.04	–0.11	0.14
VMA_1	0.02	0.81	–0.08	0.30	–0.03	0.67
VMA_2	0.01	0.92	0.11	0.12	–0.15	0.04

3. Discussion

At present, the evaluation methods of cardiac autonomic nervous system (ANS) mainly include: Neuroelectrophysiological method, plasma CA level detection, neurotransmitter analog level detection, neurotransmitter related metabolic enzymes detection, HRV. In this study, the authors combined non-invasive (HRV) and invasive (blood CA metabolite level) methods to evaluate the ANS homeostasis in OSAHS patients. HRV represents the difference between successive RR intervals during normal beating of the heart, including time domain analysis, frequency domain analysis and nonlinear analysis. In time domain analysis, SDNN reflects the balance of sympathetic parasympathetic nerve in cardiac nerve regulation, and the decrease of SDNN mainly indicates sympathetic hyperfunction; however, RMSSD and PNN50% are sensitive indicators reflecting vagus nerve tension, and their decrease indicates the decrease of vagus nerve tension[3]. HRV can evaluate the autonomic nerve regulation function at the sinoatrial node level, thus reflecting the overall balance of cardiac ans[4]. The results of this study show that the PNN50% of OSAHS patients is lower than that of non OSAHS patients, and in OSAHS patients, the PNN50% of moderate and severe OSAHS patients is lower than that of mild OSAHS patients. This result is consistent with the current studies at home and abroad[5-7]. The author believes that OSAHS patients have decreased vagal tension at night compared with non OSAHS patients.

In order to more comprehensively evaluate the cardiac ANS function level of OSAHS patients, the author also analyzed the concentration of CA and metabolites in the peripheral blood of OSAHS patients in the morning. It was found that the concentration of Mn, NMN and VMA_2 in the morning blood of OSAHS patients was significantly higher than that of non OSAHS patients. In patients with OSAHS, the levels of Mn and NMN further increased with the increase of AHI. The morning blood NMN levels in patients with severe OSAHS were significantly higher than those in patients with mild and moderate OSAHS. To some extent, it shows that the nocturnal sympathetic nerve activity of OSAHS patients is higher than that of non OSAHS patients, and the sympathetic nerve is more excited with the aggravation of OSAHS. This conclusion echoes the conclusion of the author after analyzing HRV. VMA1 and VMA_2, as metabolites of blood Ca, have no significant changes in OSAHS patients with different severity, and are not consistent with the change trend of Mn and NMN. It is considered that the psychological status, medication, diet, living habits, and even sitting or lying position during blood collection may affect the metabolism of ca. Therefore, the above possible influencing factors should be standardized in future studies to minimize their impact on the research results. The author also found that SDNN, which mainly represents the degree of cardiac sympathetic nerve activity in HRV, has no significant difference between OSAHS patients and non OSAHS patients. It is generally believed that cardiac sympathetic nerve and parasympathetic nerve (vagus nerve) are antagonistic. According to this theory, in OSAHS, the nocturnal vagal tension decreases, so the sympathetic nerve tension should also be correspondingly enhanced. However, in this study, according to HRV parameters, it is found that only vagus nerve tension decreases in OSAHS patients, however, there was no significant change in sympathetic nerve tension, which may be related to the regulation characteristics of cardiac autonomic nerve.

The cardiac sympathetic nerve mainly governs the ventricular region of the heart, and the cardiac parasympathetic nerve fibers walk in the vagusnerve. Therefore, the cardiac parasympathetic nerve is called the vagus nerve, which mainly governs the sinus node region of the heart. Although the heart is simultaneously innervated by sympathetic and vagus nerves, according to the distribution of cardiac autonomic innervation and pharmacological effects, under normal circumstances, the vagus nerve is dominant in autonomic innervation of cardiac electrical activities, and this dominant effect is more obvious at night. In this study, according to the comprehensive analysis of HRV and blood Ca, the author believes that OSAHS patients have obvious cardiac autonomic nerve disorder, decreased vagal tension and increased sympathetic excitation. However, when OSAHS has an impact on the nocturnal autonomic nerve homeostasis of patients, its impact on the vagus nerve is greater than its impact on the sympathetic nerve. During sleep, the decrease of the vagus nerve tension in OSAHS patients is more obvious than that of the sympathetic nerve excitation. Therefore, in this study, the PNN50% change of the vagus nerve tension is more obvious, and the SDNN indicating the degree of sympathetic hyperfunction has no significant change in the two groups of patients. The main manifestation of cardiac autonomic nerve disorder in OSAHS patients is the decrease of vagus nerve tension the dominant advantage of the vagus nerve over the sympathetic nerve in OSAHS patients is weakened, and this advantage will be further weakened with the serious aggravation of the disease. At the same time, the protective effect of the vagus nerve on the cardiovascular system will also be weakened. The autonomic nervous regulation of the heart has an important impact on the process of adverse cardiovascular events. The increase of vagal activity has a protective effect on the heart through a variety

of direct and indirect mechanisms, including antiinflammatory, inhibition of structural remodeling and electrical remodeling[8]. In previous studies on the relationship between OSAHS and cardiovascular disease, more attention was paid to the role of sympathetic hyperexcitability in the occurrence and development of cardiovascular adverse events, and the impact of decreased vagal tension on the cardiovascular system was often ignored. In the correlation analysis, AHI in OSAHS patients was negatively correlated with SDNN and

PNN50%, but positively correlated with NMN. The age of OSAHS patients was negatively correlated with SDNN, RMSSD, PNN50%, but positively correlated with NMN. The age-related trend is basically similar to AHI, a landmark indicator of OSAHS disease severity, indicating that the severity of OSAHS increases with age. The author believes that the further weakening of the regulatory advantage of nocturnal vagus nerve in OSAHS patients with age may be related to the high incidence of cardiovascular disease.

Sinus node pacemaker cells autonomously generate action potentials and reach cardiomyocytes through the conduction system to control the rhythm and contraction of the heart. As sinus node autonomic cells, P cells have no platform phase, only 0,3,4 phases of action potentials. When the automatic depolarization of phase 4 reaches the threshold potential level, action potentials can erupt. The mechanism of 4-phase automatic depolarization of P cell action potential involves two aspects: The weakening of outward current and the enhancement of inward current. Among them, delayed rectifier potassium current (IK), hyperpolarization activated inward ion current (if) and T-type calcium current (ica-t) are more important. Sympathetic nerve acts on β Adrenergic receptor enhanced if and ica-t to produce positive chronotropic effect. Acetylcholine secreted by vagus nerve activates acetylcholine sensitive potassium current (IK ach) through M-type cholinergic receptor to cause hyperpolarization of P cell membrane. At the same time, by inhibiting the activation of adenylate cyclase, the production of camp is reduced, and then the phosphorylation of calcium channel is inhibited. As a result, the calcium current (ICA) is reduced. Both of them have a negative chronotropic effect, that is, decreased autonomy[9]. The exact mechanism of the decrease of cardiac vagal tone caused by OSAHS is not clear, but intermittent hypoxia in OSAHS patients will activate systemic inflammatory response and increase inflammatory mediators, including various factors, complement and oxygen free radicals, such as IL-1, IL-6 and TNF[10]. The authors believe that inflammatory mediators may play a role by affecting the production of vagal neurotransmitters, presynaptic plasticity and neurotoxicity, and ultimately affect the regulation of the vagal nerve on the heart. The mechanism needs further study.

Conflict of interest

The authors declare no conflict of interest.

References

1. Khayat R, Pleister A. Consequences of obstructive sleep apnea. Sleep Medicine Clinics, 2016, 11(3): 273.
2. Sleep disordered breathing group, respiratory branch, Chinese Medical Association Guidelines for the diagnosis and treatment of obstructive sleep apnea hypopnea syndrome (2011 Revision). Chinese Journal of tuberculosis and respiration, 2012,35 (1): 9.
3. Chen E. Research and application progress of heart rate variability. Progress in cardiology, 2014,35 (4): 435.
4. Kivinieml AM, Hautala AJ, Mokikallio TH, et al. Cardiac vagal outflow after aerobic training by analysis of high-frequency oscillation of the R-R interval. European Journal of Applied Physiology, 2006,96: 686.
5. Song MK, Ha JII, Ryu SH, et al. The effect of aging and severity of sleep apnea on heart rate variability indices in obstructive sleep apnea syndrome. Psychiatry Investig, 2012, 9(1): 65.
6. Zhong X, Xiao Y, Huang R. Effects of obstructive sleep apnea hypopnea syndrome on vascular endothelial function and autonomic nerve modulation. Journal of Chinese Academy of Medical Sciences, 2010,32 (002): 162.
7. Ma Y, Wen H, Zeng X, et al Analysis of arrhythmia and heart rate variability in patients with obstructive sleep apnea syndrome. Chinese Journal of cardiac pacing and electrophysiology, 2019,33 (2): 34.
8. Ji M, Zhou Q. Research progress of vagal activity in heart failure. Chinese Journal of cardiac pacing and electrophysiology, 2012,26 (6): 547.
9. Zhu D, Wang T. Physiology. 8th Edition Beijing: People's Health Publishing House, 2013:100.
10. Iturriaga R, Oyarce MP, Dias ACR. Role of carotid body in intermittent hypoxia-related hypertension. Curr hypertensrep,2017,19(5):38.