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Computerized Heart Rate Analysis in the Selection of Therapy for Patients With Arterial Hypertension

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ABSTRACT

According to the World Health Organization (WHO), over 1 billion people are overweight and 600 million are obese, with metabolic syndrome (MS) affecting 35% of adults in the US and 20-25% in Europe. MS patients require appropriate therapy with comorbidity in mind, which requires further study and optimization. Analysis found changes in HF, LF, and ULF domains of HRV spectrum, indicating transition to a more energy-intensive level of control and depletion of regulatory mechanisms which allow to detect latent disorders of regulatory mechanisms (with seeming clinical well-being) in patients with MS. The control of ULF%, VLF% and IC index by HM-ECG method allows to change the therapy in time and to obtain a better result.

Keywords: Metabolic syndrome, Holter ECG monitoring, β-blockers, Computer analysis of the wave spectrum

INTRODUCTION

Arterial hypertension (AH) typically accompanies conditions like abdominal obesity, insulin resistance, and metabolic disturbances, rather than existing alone (Uspensky et al., 2017). Acknowledged as a 21st century pandemic, metabolic syndrome amplifies cardiovascular risk when combined with AH (Korotkova, 2014; Bloomgarden, 2006; Sprecher and Pearce, 2000; Isomaa et al., 2001). AH's pathogenesis involves autonomic dysfunction, particularly hyperreactive sympathetic nervous response, making selective β-blockers an effective treatment (Agasarov, 2019; Kobalava and Tolkacheva, 2005). Metabolic disturbances exacerbate this dysfunction by inducing autonomic neuropathy.

Monitoring autonomic regulation and its response to therapy could be key in predicting therapeutic effect and drug selection. Heart rate variability (HRV) analysis, a non-invasive method, assists in evaluating the body's functional state and regulatory mechanisms (Baevsky et al., 2001). As per the European Society of Cardiology and the North American

Society of Electrophysiologists, reduced HRV in patients with coronary artery disease (CAD) independently predicts higher risk of severe ventricular arrhythmias and sudden death post-myocardial infarction (Shestakova, 2009; Bigger et al., 1993).

Yet, the primary dysfunction in the autonomic nervous system in metabolic syndrome patients—whether sympathetic or parasympathetic—and the influence of β-blockers at various levels remain undetermined.

The aim of this study was to assess the influence of β-blockers on heart rate variability in patients with metabolic syndrome.

MATERIALS AND METHODS

The study was conducted at the Federal State Educational Institution of Higher Education "Patrice Lumumba Russian University of Friendship of Peoples" at the clinical bases of the Department of Hospital Therapy with courses in endocrinology, hematology, and clinical laboratory diagnostics during the period from 2020 to 2023. The work was carried out in accordance with the plan of scientific research work, observing the principles of medical bioethics (approval form of the ethics committee of the RUDN Medical Institute No. 5 of March 17, 2022).

Criteria for including patients in the study:

- age 40-74;
- patients with obesity of varying degrees;
- arterial hypertension in medical history;
- patients with diabetes;
- patients with dyslipidemia;
- patient's informed consent to participate in the study.

Criteria for excluding patients from the study:

- age <40 and >74 years old;
- absence of informed consent;
- acute cardiovascular events at the time of the study;
- persistent decompensation of diabetes;
- chronic heart failure more than 2 degrees

A total of 166 patients were examined, 150 patients in inpatient conditions, and 16 patients in outpatient conditions. The main reason for hospitalization of patients included in the study was high blood pressure, obesity of the 2nd and 3rd degrees, and type 2 diabetes.

All patients were divided into two major groups - patients with metabolic syndrome (n = 121), Observation Group 1, and patients with normal body weight (n = 45), Comparison Group 2. Metabolic syndrome was diagnosed based on the ATP III risk criteria (Dobrowolski et al., 2022).

Since patients with arterial hypertension (AH) often received antihypertensive therapy with beta-blockers, it seemed appropriate to divide patients into groups based on this characteristic. All patients with metabolic syndrome, depending on the therapy received, were divided into two subgroups: subgroup "A" - patients receiving beta-blockers, and subgroup "B" - patients not receiving beta-blockers.

Subsequently, in patients with metabolic syndrome (MS), the state of metabolic and autonomic regulation was also assessed at each stage of metabolic syndrome development, i.e., depending on the degree of abdominal obesity (A1, A2, A3, A4, and similarly in subgroup "B").

The comparison group (subgroups "C" and "D") included patients with normal body weight and arterial hypertension, but without abdominal obesity. This approach allowed us to assess the contribution of obesity to the dysfunction and regulation of the autonomic nervous system and the impact of beta-blockers on the state of these mechanisms, and therefore, on the development and progression of cardiovascular diseases in the compared groups of patients.

The complete examination included: medical history collection, physical examination, blood pressure measurement, standard biochemical tests, ECG recording, echocardiography, and 24-hour ECG monitoring.

Heart rate variability (HRV) was assessed with the help of the Valenta MN-02-8 hardware-software complex, calculating the generally accepted time and spectral HRV indicators according to the European Society of Cardiology and the North American Society of Electrophysiology. The studied HRV indicators by spectral characteristics are presented in Table 1. Patients underwent 24-hour ECG monitoring in hospital conditions.

Table 1. HRV indicators.

Studied HRV (Heart Rate Variability) indicators for 24 hours of ECG recording	
Indicators	Definition
ULF, ms^2	Power in the ultra-low frequency range (less than 0.003 Hz)
VLF, ms^2	Power in the very low frequency range (0.003–0.04 Hz)
LF, ms^2	Power in the low frequency range (0.04–0.15 Hz)
HF, ms^2	Power in the high frequency range (0.15–0.40 Hz)
LF/HF	Ratio of low to high frequency power values in absolute terms

METHODS OF STATISTICAL PROCESSING OF RESEARCH RESULTS

For statistical data processing, Statistica software (version 10) was used. Distribution testing was performed using the Shapiro-Wilk W-criterion. For quantitative variables with a normal distribution, the arithmetic mean (M) and standard deviation (SD) were calculated, and for quantitative variables with an asymmetric distribution (Skewness>1) - the median (Me) and interquartile range (IQR). The Student's t-test was used to verify the reliability and differences between two groups with a normal distribution, and the Mann-Whitney U-test was used for a non-normal distribution. For three independent groups, the Kruskal-Wallis criteria were used. Qualitative variables are presented as absolute (n) and relative (%) values. The Pearson's chi-square test ($\chi 2$) was used to compare groups in terms of the frequency of qualitative variables. Results were considered statistically significant at two-sided p values < 0.05. Comparison of two groups by a quantitative indicator, the distribution of which differed from normal, was performed using the Mann-Whitney U-test.

RESULTS

In the group of examined patients with metabolic syndrome (arterial hypertension and excess body weight or obesity), coronary heart disease (CHD) was noted in 25.9% of patients, which is almost twice as often as in the comparison group (with arterial hypertension and normal body weight) — 15.6% of cases. We analyzed the frequency of CHD in Group A patients depending on the degree of obesity. And it turned out that results comparable to those of Group B were observed only in patients with excess body weight (BMI 25–29.9 kg/m^2 - Group A1), where the frequency of CHD was 6.9%, but with each subsequent stage of obesity, this indicator increased progressively (Fig. 1).

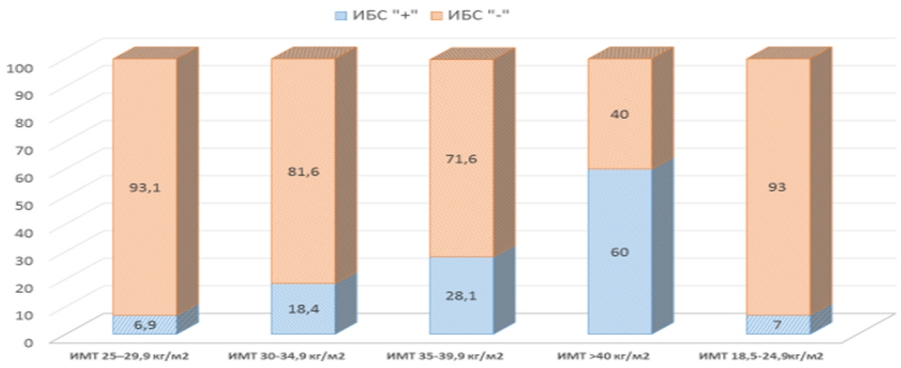

Figure 1: Diagram of the prevalence of CHD depending on the degree of obesity.

In the group of patients with obesity of grade I, this indicator was already 18.4%, and in the group with morbid obesity (BMI ≥ 40kg/m^2) — already 60%.

All patients were under outpatient observation, so the main clinical and biochemical indicators, including the lipid spectrum of serum, were within acceptable values, and there were no significant differences in subgroups. In the echocardiographic study of patients with MS, 58 (75%) people had symmetric hypertrophy of the left ventricle, in the group of patients without MS slightly less - 27 (64%). The global and local contractile function of the left ventricle was normal in all patients. The average ejection fraction was 65.0±5.4%.

As a result of the conducted 24-hour ECG monitoring, not only temporal but also frequency indicators were evaluated in both compared groups (receiving and not receiving β-blockers) (Table 2, 3). More significant changes occurred when evaluating frequency characteristics.

In the subgroups of patients with MS receiving β-blockers (group "A"), there were no significant differences in the indicators of the frequency and time spectrum of HRV depending on the degree of obesity. There were also no significant differences compared to the indicators of patients without obesity taking drugs.

Table 2. Comparison of patient groups depending on the increasing body mass and taking beta-blockers.

Indicators	Group C (n - 25) Normal without obesity	Group 1A (n - 25) Overweight	Group 2A (n - 25) Obesity of 1st degree	Group 3A (n - 12) Obesity of 2nd degree	Group 4A (n - 15) Obesity of 3rd degree
ULF%	25 [23; 28]	23 [20; 25]	23 [19; 27]	22 [9; 27]	20 [11; 23]
P1(C;1A)= 0,160; P2(C;2A)=0,360 ; P3(C;3A)=0,100; P4(C;4A)=0,004; P5(1A2A)=0,810; P6(1A3A)= 0,860; P7(1A4A)=0,050 ; P8(2A3A)=0,970 ; P9(2A4A)=0,080; P10(3A4A)=0.340					
VLF%	59 [53; 61]	60 [51; 64]	60 [51; 63]	57 [48; 62]	50 [47; 60]
P1(C;1A)=0,420 ; P2(C;2A)=0,700 ; P3(C;3A)=0,930 ; P4(C;4A)= 0,030; P5(1A2A)=0,750; P6(1A3A)=0,510 ; P7(1A4A)=0,040 ; P8(2A3A)=0,700 ; P9(2A4A)=0,050 ; P10(3A4A)=0,510					
LF%	6 [4 ; 8]	6 [4 ; 12]	8 [4 ; 12]	8 [5 ; 19]	9 [7; 17]
P1(C;1A)=0,610 ; P2(C;2A)=0,340 ; P3(C;3A)=0,120; P4(C;4A)=0,030 ; P5(1A2A)=0,710; P6(1A3A)=0,350; P7(1A4A)=0,070; P8(2A3A)=0,480; P9(2A4A)=0,290 ; P10(3A4A)=0,740					
HF%	12 [7 ;17]	10 [5 ;17]	10 [6 ;18]	13 [7; 24]	21 [11; 26]
P1(C;1A)= 0,830; P2(C;2A)=0,740; P3(C;3A)=0,790; P4(C;4A)=0,020 ; P5(1A2A)=0,950; P6(1A3A)=0,960 ; P7(1A4A)=0,020 ; P8(2A3A)= 0,880; P9(2A4A)=0,008 ; P10(3A4A)=0,160					
LF\HF	1 [0,25; 1,0]	1 [0,5; 1]	1 [1; 1]	1 [1 ; 1]	0,5 [0,3; 1]
P1(C;1A)= 0,500 ; P2(C;2A)=0,490; P3(C;3A)=0,160; P4(C;4A)=0,700; P5(1A2A)=0,600; P6(1A3A)=0,160; P7(1A4A)=0,840 ; P8(2A3A)= 0,250; P9(2A4A)=0,110 ; P10(3A4A)=0,040					
IC	5 [4 ; 10]	7 [3; 14]	7 [4 ; 11]	5 [3 ; 10]	3 [2; 6]
P1(C;1A)= 0,950 ; P2(C;2A)=0,640; P3(C;3A)=0,870; P4(C;4A)=0,030; P5(1A2A)=0,890; P6(1A3A)=0,640 ; P7(1A4A)=0,020 ; P8(2A3A)=0,95 ; P9(2A4A)= 0,010 ; P10(3A4A)=0,040					

Note: Data are presented as median, 25th and 75th percentile, as (Me (IQR)) or arithmetic mean (M) and standard deviation of the mean (SD).

Table 3. Comparison of patient groups depending on body mass index not taking beta-blockers.

Indicators	Group 2D (n -20) Normal body weight	Group 1B (n -11) Overweight	Group 2B (n -10) Obesity of 1st degree	Group 3B (n -10) Obesity of 2nd degree	Group 4B (n -13) Obesity of 3rd degree
ULF%	51[37; 63]	65 [51; 75]	11 [8 ; 18]	61[25; 64]	42[38; 55]
P1(D;1B)=0,07 ; P2(D;2B)= 0,0001; P3(D;3B)=0,58; P4(D;4B)= 0,27; P5(1B2B)= 0,00003; P6(1B3B)=0,09 ; P7(1B4B)= 0,008 ; P8(2B3B)=0,00002 ; P9(2B4B)=0,00001 ; P10(3B 4B)=0,34					
VLF%	23[17; 39]	14 [12 ; 20]	16 [13; 52]	25[11; 27]	17[11; 21]
P1(D;1B)=0,03 ; P2(D;2B)= 0,123; P3(D;3B)=0,70 ; P4(D;4B)= 0,04; P5(1B2B)= 0,0004; P6(1B3B)=0,16; P7(1B4B)= 0,985 ; P8(2B3B)= 0,0310 ; P9(2B4B)= 0,270 ; P10(3B 4B)= 0,229					
LF%	8 [4,6 ; 16]	6 [5; 11]	19 [18; 28]	6 [6; 13]	11 [7; 24]
P1(D;1B)= 0,36; P2(D;2B)=0,00003; P3(D;3B)= 1,000 ; P4(D;4B)=0,19 ; P5(1B2B)= 0,00001; P6(1B3B)=0,04; P7(1B4B)= 0,002 ; P8(2B3B)= 0,0050 ; P9(2B4B)= 0,023 ; P10(3B 4B)= 0,229					
HF%	6,3 [6; 14]	12 [6; 20]	38 [19; 60]	9 [6 ; 21]	21[9 ; 30]
P1(D;1B)=0,28; P2(D;2B)= 0,00003; P3(D;3B)=0,35 ; P4(D;4B)=0,001 ; P5(1B2B)=0,0001 ; P6(1B3B)= 0,92; P7(1B4B)=0,026 ; P8(2B3B)= 0,00005 ; P9(2B4B)= 0,002; P10(3B 4B)= 0,025					
LF\HF	1 [1 ; 2]	0,5 [0,4; 1]	0,8[0,3 ; 1]	1 [0,5; 1,4]	1,1 [0,3; 1,2]
P1(D;1B)=0,01; P2(D;2B)= 0,0004; P3(D;3B)=0,54 ; P4(D;4B)=0,09 ; P5(1B2B)=0,87 ; P6(1B3B)= 0,06; P7(1B4B)= 0,50 ; P8(2B3B)= 0,009 ; P9(2B4B)=0,097 ; P10(3B 4B)= 0,598					
IC	5 [2; 10]	1 [1 ; 7]	1 [1 ; 4]	4[2,3; 6,1]	2 [1; 3]
P1(D;1B)= 0,12; P2(D;2B)= 0,001 ; P3(D;3B)= 0,23; P4(D;4B)=0,02 ; P5(1B2B)= 0,05 ; P6(1B3B)=0,92 ; P7(1B4B)=0,80 ; P8(2B3B)=0,01 ; P9(2B4B)= 0,138 ; P10(3B 4B)= 0,229					

Note: Data are presented as median, 25th and 75th percentile, as (Me (IQR)) or arithmetic mean (M) and standard deviation of the mean (SD).

In patients with metabolic syndrome who did not take β-blockers (group "B"), HRV changes different from the indicators of patients not taking them were detected already in the group of patients with excess body weight (B1). And in each group with a higher degree of obesity, the differences in the indicators became more and more significant ($p < 0.001$) compared to patients taking β-blockers (Table 3).

Starting from the second degree of obesity, the frequency spectrum in patients of group "B" shifted towards an increase in the ULF (%) and VLF (%) indicators. A high level of reliability of the correlation relationship with the body mass index we got for the indicators VLF% ($r = 0.350$, $P < 0.003$) and LF% ($r = 0.56$; $P < 0.033$), as well as with the coefficient of vagosympathetic balance LF/HF ($r = 0.413$; $P < 0.0001$). ULF (%) reflects the influence of higher suprasegmental centers of autonomic regulation. The average value of ULF indicators changed depending on the degree of obesity. The minimum values were found in patients with obesity of grade I (group B2), in which the indicator was $18.7 \pm 5.5\%$. The maximum ULF indicator was in patients with obesity of grade II (subgroup B3), the average value of which was $40.1 \pm 3.2\%$. Since ULF reflects the activity of higher regulation centers (their involvement in maintaining regulatory processes, the translation of regulatory mechanisms from the level of "control" to the level of "centralization"), the state of exhaustion of reserves and breakdown of adaptation, which fully explains the increased risk of cardiovascular events in this group of patients. Therefore, it can be confidently said that in patients with metabolic syndrome, the risk of developing CVD becomes high with the presence of grade II obesity and is largely due to a violation of autonomic regulation.

The average duration of patient observation was 2 years. During the observation period, acute cardiovascular events were noted in the group of patients with metabolic syndrome receiving β-blockers - 4 cases (5.2%), in the group of patients not taking these drugs - 4 cases (9.1%), in the group of patients without obesity taking β-blockers (group C), this indicator was also better compared to the group taking other combinations of antihypertensive drugs (group D) - 4% versus 10%.

DISCUSSION

The main question to be answered in accordance with the purpose of the study is not only how obesity affects the functioning of such an important regulatory system as the autonomic nervous system, and, if "yes", then from which degree of obesity this influence becomes significant, but also to assess the importance of autonomic dysregulation in increasing cardiovascular risk for this group of patients.

Some indicators characterizing the state of autonomic regulatory mechanisms can be used to predict the progression of metabolic syndrome (MS) and assess cardiovascular risk. In patients with abdominal obesity, starting from the 2nd degree, the values of ULF% and VLF% indicators reliably increased. LF reflects the activity of higher regulation centers (their involvement in maintaining the regulatory processes, the transfer of regulatory mechanisms from the level of "control" to the level of "centralization"), the state of exhaustion of reserves and the failure of adaptation, which fully explains

the increased risk of cardiovascular events in this group of patients. Therefore, it can be confidently said that in patients with metabolic syndrome, the risk of developing cardiovascular diseases becomes high in the presence of 2nd degree obesity and is largely due to the disruption of autonomic regulation. The data obtained from the study allow us to identify two stages in the development of arterial hypertension against the background of metabolic syndrome, increasing the risk of developing cardiovascular complications. The fact that the risk significantly increases in patients with 2nd degree obesity is known from other studies as well, but we would like to draw attention to the fact that similar risks appear in patients at the stage of transition from 1st degree obesity to 2nd degree. Disruptions of regulatory mechanisms begin earlier, and for a long time they proceed covertly, due to the increased tension of adaptation mechanisms and reach the metabolic level only when the regulatory mechanisms are exhausted (centralization level).

β-blockers have a pronounced positive effect on the dynamics of the disease and reduce the risk of developing cardiovascular diseases. The main indicators of heart rate variability in patients with MS taking beta-blockers did not have significant differences from the indicators of patients without obesity, which reduced the frequency of acute cardiovascular events to a comparable level.

CONCLUSION

1. Directly β-blockers have a pronounced positive effect on heart rate variability in patients with metabolic syndrome.
2. Patients with metabolic syndrome (especially those patients who have 1st degree obesity) are recommended to prescribe β-blockers (selective) for the prevention of cardiovascular diseases.

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