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HEART RATE VARIABILITY IN PATIENTS WITH CHRONIC HEART FAILURE AND METABOLIC SYNDROME

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Abstract
The features of heart rate variability in patients with chronic heart failure were analyzed depending on the presence of metabolic syndrome components. 106 patients with functional class II-III chronic heart failure caused by postinfarction cardiosclerosis were examined. The study of the state of heart rate variability was carried out using Holter ECG monitoring.

Keywords: Chronic heart failure, metabolic syndrome, heart rate variability.

Introduction

The prevalence of chronic heart failure (CHF) among the population of most countries of the world is 1-3% in people under 70 years of age and increases to 10% in people over 70 years of age [1,4,5,8,9]. Despite modern methods of treatment, CHF continues to spread, worsening the socio-economic aspects of patients' lives, limiting their physical abilities, reducing their emotional perception of life. Studies conducted in various countries of the world have shown that approximately 6.5 million people in Europe, 5 million in the USA and 2.4 million in Japan suffer from CHF. In Russia, at least 3-3.5 million people have

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reduced function of the left ventricle (LV) and obvious symptoms of decompensation [1,6,7,9].

The modern model of the pathogenesis of CHF considers it as a pathology of neurohumoral mechanisms of blood circulation regulation. It is generally believed that a violation of the pumping function of the heart in CHF and a decrease in cardiac output, leading to a decrease in blood pressure (BP), causes activation of the sympathetic nervous system (SNS), resulting in tachycardia and peripheral vasoconstriction [4,7,8].

In the development of these disorders, extra-cardiac factors are also important, the most important of which is the metabolic syndrome (MS), which is considered a classic cluster of components that aggravates the severity of the course of CVD [1,2,3,5].

The simplest indicator of the influence of the autonomic nervous system (ANS) on cardiac activity is the heart rate (HR) during the day. A more complete picture of the influence of the ANS on cardiac activity is given by the method of determining heart rate variability (HRV), which reflects a complex picture of various control influences on the circulatory system with interference of periodic components of different frequencies and amplitudes, with the nonlinear nature of the interaction of different levels of control [11,12,13,14].

Based on the above data, the **aim** of this study was: to study the features of heart rate variability in patients with chronic heart failure FC II-III, depending on the representation of the components of the metabolic syndrome.

Materials and methods of research:

We examined 106 male patients with postinfarction cardiosclerosis with a history of myocardial infarction from 6 months to 5 years, with chronic heart failure II-III functional class (FC) according to NYHA [3]. Considering the components of MS, the patients were divided into three groups:

1st group of patients with CHF FC II-III (n=35) had only 2 signs of MS, of which DLP+TG (n=6, 17.2%), AH+DLP (n=7, 20%), AH+AO (n=7, 20%), AG+DM type2 (n=7, 20%), DM type 2+DLP (n=8, 22.8).

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Patients of the 2nd group with CHF FC II-III (n=36) together with established dyslipidemia (DLP) had the following combinations of MS components: DLP+TG+AH (n=13, 36.1%), DLP+TG+AH+AO (n=9, 25%), DLP+AO+AH (n=14, 38.9%).

3rd group of patients with CHF FC II-III (n=35), who in addition to type 2 diabetes mellitus (DM2) had the following components of MS: DM2+DLP+AH (n=8, 22.15%), SD2+DLP+AH+AO (n=9, 25%), DM2+TG+AO (n=8, 22.15%), DM2+AH+AO (n=10, 27.7%).

We used the criteria for the diagnosis of MS of the International Diabetes Federation (IDF, 2009). The main components of MS were considered: abdominal obesity (AO) (>94 cm for men); TG level (>1.7 mmol/L); HDL level (<1.03 for men); blood pressure level (SBP >130 mmHg.st; DBP >85 mmHg), fasting glucose level (>5.6 mmol/L) or the presence of type 2 diabetes mellitus [2,3].

The examined patients were hospitalized in the Department of Cardiology of the Republican specialized scientific and practical medical center for therapy and medical rehabilitation of the Republic of Uzbekistan, Tashkent. The HRV condition was studied using Holter monitoring of the daily ECG. To register and analyze the ECG, the installation of the "Cardio Sens" system (KHAI-Medika, Kharkiv) and the software of the same company were used.

Criteria developed by the working group of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology were used to assess HRV. The following time analysis indicators were analyzed: mRR (ms)–(mean RR) the average value of all RR intervals (the inverse of the average heart rate); SDNN (ms) – (standard deviation), the standard deviation of all analyzed RR intervals; SDNNi (ms) – the average value of standard deviations of RR intervals calculated for all 5-minute sections of ECG recording; SDANN (ms) – (standard deviation of all mean 5-minute normal sinus intervals over 24 hours) standard deviation from the average durations of RR intervals calculated on all 5-minute sections of ECG recording; rMSSD (ms) (square root of the mean of the sum of the squares of differences between adjacent normal R-R intervals), the root–mean-square difference between the duration of adjacent RR intervals;

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pNN50 (%) - (percentage of successive intervals differing by more than 50 ms), the percentage of episodes of difference of consecutive RR intervals by more than 59 ms. The general tone of the autonomic nervous system reflects SDNN, MRR, HRV TI and TP; the tone of the parasympathetic system - pNN50 and r-MSSD, the sympathetic system – SDANN [13,14].

The main vector of HRV assessment consists of two polar directions: an increase in the parameters of the time analysis of HRV is associated with an increase in parasympathetic influences, and a decrease is associated with the activation of sympathetic tone. The general tone of the ANS reflects SDNN, the tone of the parasympathetic system - pNN50 and r-MSSD, the sympathetic system – SDANN [11,12,13].

Spectral or frequency analysis of HRV (frequency domain) implies the separation of the processed sample (the number of analyzed intervals for a certain time) RR intervals, using autoregressive analysis into frequency spectra of different densities. Frequency analysis allows you to determine the maximum total power of the spectrum (S2/Hz), the spectral powers of the high frequency (High Frequency, HF), low Frequency (Low Frequency, LF) and ultra-low frequency (Very Low Frequency, VLF) components (frequency range 0.15-0.35 Hz, 0.05-0.15 Hz and 0.004-0.05 Hz, respectively), as well as the ratio (index) LF/HF – the ratio of power values in absolute values. It also makes it possible to assess the balance of sympathetic and parasympathetic influences on the activity of the sinus node [12,13].

Statistical processing of the obtained research results was carried out on an IBM PC/AT type personal computer using the package of the standard electronic program "biostatic for Windows, version 4.03". The parameters were described as M±δ. In the distribution of values, group comparisons of quantitative variables were carried out using the Student's variational statistical criterion (t).

The results of the study and their discussion

The results of the analysis of the clinical characteristics of patients with CHF FC II-III and MS showed that all the examined patients were comparable in age and prescription of the disease. Patients of the 3rd group of the study had high LDL,

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TG and atherogenicity coefficient and fasting glucose levels compared with the data of the 1st group of the study ($p<0.05$). The results of the analysis of clinical indicators are presented in Table No. 1.

Table № 1. Clinical characteristics of the examined patients.

Indicators	I Group (n=35)	II Group (n=36)	III Group (n=35)
Age, years	56,38±5,60	54,14±6,31	58,92±4,6
Disease duration, years	4,38±1,74	5,71±3,25	6,15±3,74
MI prescription, years	2,66±1,33	5,00±2,21*	4,46±1,31*
Total cholesterol, mmol/l	5,72±0,44	5,95±0,46	6,30±0,51
HDL, mmol/l	1,34±0,19	1,48±0,30	1,37±0,38
LDL, mmol/l	3,48±0,52	4,95±0,48*	4,53±0,45*
TG, mmol/l	2,29±0,54	2,76±0,36	2,94±0,44*
Atherogenicity coefficient	2,92±0,31	3,41±0,24*	3,45±0,34*
Fasting glucose, mmol/l	5,21±0,32	4,89±0,49	7,18±0,52*
Waist circumference, sm	93,75±2,47	98,86±3,8	100,23±4,01
BMI, kg/m^2	26,5±2,6	27,84±3,3	28,8±4,3
SBP, mmHg	138,5±7,8	137,6±7,6	143,2±8,4
DBP,mmHg	89,4±5,5	88,9±6,7	93,4±8,2

Note: * $p<0.05$ - compared to the indicators of the 1st group.

According to the HRV analysis of the 24-hour ECG recording (Table No. 2), in contrast to the data of the control group, in the groups of patients with CHF and MS, there was a significant decrease in all time and frequency HRV indicators. A significant decrease in HRV in the groups of patients with CHF and MS occurred due to a significant decrease in the parasympathetic influence of the ANS (low values of rMSSD, pNN50, HF, mc2 and HF norm). A statistically significant decrease in the total HRV capacities (mRR, HRV TI, TP) indicating the overall activity of the ANS was also revealed. More pronounced changes were detected in the 2nd and 3rd groups of patients ($p<0.01$). The results of the analysis are presented in Table No. 2.

The results of the analysis of HRV indicators of patients of the 2nd group showed lower indicators of total HRV in relation to the results of HRV of the 1st group of

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the study. In particular, a significant decrease in mRR, TR and the triangular index - HRV TI by 14.8% was revealed, which reflect the total HRV power ($p<0.05$). In the 2nd group of patients, in contrast to the 1st group, low values of SDNNi, rMSSD, pNN50 indicators remained, which indicates the absence of expansion of the parasympathetic part of the spectrum in these patients ($p<0.05$). Low indices of parasympathetic effects of the nervous system SDNNi by 13.7%, rMSSD ms by 28.4%, rMSSD% by 34.7% and pNN50 by 30.6% were revealed in relation to the data of the 1st group. There were low indicators of sympathetic effects of SDANN by 12.0% ($p<0.05$). The results of HRV analysis with daily ECG monitoring are presented in Table No. 2.

Table №.2. HRV indicators in patients with CHF and MS.

Indicators	I Group (n=35)	II Group (n=36)	III Group (n=35)
mRR, ms	723,88±17,24	658,1±21,7*	601,29±24,26**
SDNNi, ms	48,80±3,5	42,9±4,5*	40,64±3,9*
SDANN, ms	133,5±9,3	149,5±11,4*	150,3±8,9*
pNN50, ms	8,1±1,5	6,2±1,1	5,7±1,2*
RMSSD, ms	42,50±6,12	33,14±5,27*	30,8±6,4**
RMSSD%	11,06±2,05	7,59±3,08	6,8±3,2*
HRV TI, u	30,75±5,51	26,6±4,8	25,70±4,51*
TP, ms^2	3198,63±62,54	2884,2±58,7*	2923,14±57,26*
ULF, ms^2	1085,13±127,61	989,8±103,4	950,0±125,07
VLF, ms^2	794,63±66,76	732,2±73,5	629,43±58,67
LF, ms^2	633,25±64,46	697,29±65,04	794,8±59,4*
LF norm, %	63,74±10,0	61,94±8,27	85,9±11,6*
HF, ms^2	385,38±43,73	297,57±41,09*	282,0±29,9**
HF norm, %	32,26±6,2	28,06±4,27	26,1±5,6*
LF/HF, u.	2,46±0,26	2,65±0,38	3,0±0,25*

Note: * $p<0.05$; ** $p<0.01$ compared to the indicators of the 1st group,

Spectral analysis of HRV in the 2nd group of the study revealed an insignificant increase in low-frequency oscillations characterizing the sympathetic influence of the ANS: LF, ms2 and LF norm, % by ($p>0.05$). There was a significant decrease in the vagal effects of ANS: HF, ms2 by 29.6% ($p<0.05$). An increase in

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sympathetic influences and a decrease in vagal activity in group 2 patients was accompanied by a slight increase in the LF/HF ratio, towards the relative predominance of SNA (2.65±0.38 vs. 2.46±0.26; $p<0.05$) in group 2 patients compared to group 1, in which the level of the LF component and the LF/HF ratio corresponded to a more balanced state of the autonomic nervous system.

The results of the analysis of the heart rate variability of 24-hour ECG recording in patients with CHF and MS revealed a decrease in the total HRV power in the 3rd group of CHF patients with MS, who had DM2, which was manifested by a decrease in the average value of all RR intervals (mRR) by 20.4% and the average value of standard deviations of RR intervals (SDNNi) 21.2% compared with HRV data of the 1st group of the study ($p>0.05$).

When analyzing vegetative regulation in patients of group 3, a persistent decrease in HRV was revealed, which was manifested by significantly low values of the triangular HRV TI index by 19.2%, as well as the total power of the TP spectrum by 13.7% compared with the 1st group of the study ($p<0.05$). A significant decrease in HRV in the 3rd group of the study also occurred due to a significant decrease in the influence of the parasympathetic part of the ANS, which was manifested by significantly low values of rMSSD by 37.9%, rMSSD% 57.2% and pNN50 by 39.4% ($p<0.05$). This condition in group 3 patients is associated with a decrease in high-frequency vagal effects on the heart rhythm.

According to the spectral analysis of HRV of the 3rd group of the study, the high frequency component of the daily HRV (HF, ms2 and HF norm, %) had a similar trend to decrease ($p<0.05$). There was a decrease in HF, ms2 by 36.5% and HF norm by 23.1% compared to the data of the 1st group of the study. In parallel with these changes, significantly high rates of low-frequency oscillations of HRV LF, ms2 by 25.4% and LF norm, % by 36.3% ($p<0.05$) were noted in this group. A significant decrease in vagal and an increase in sympathetic influences on the heart rhythm led to a significant shift in the sympathovagal index towards the predominance of SNS. Thus, the LF/HF index was 3.0±0.25 versus 2.46±0.26 ($p<0.05$).

According to the results of the analysis of HRV parameters in patients of the 2nd and 3rd groups with CHF and MS, slight fluctuations in the spectral powers of

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VLF and ULF (p>0.05) were revealed. The physiological oscillation in the very low-frequency VLF range and the ultra-low-frequency ULF range has not yet been sufficiently studied. Some authors believe that the VLF and ULF components are based on the activity of the SNA. However, in this case, it should also be considered that the fluctuations of these spectra are closely related to the psycho-emotional stress and the functional state of the cerebral cortex, which depend on the influence of the suprasegmental level of regulation.

Thus, in group 2 patients with CHF and MS, in combination of dyslipidemia, it was revealed that along with a decrease in HRV, there is a decrease in the vagal effects of ANS (pNN50, RMSSD, HF). A decrease in the total HRV capacity in patients of the 2nd group of the study was accompanied by high indicators of sympathetic effects of ANS (SDANN, LF, LF/HF). According to studies in this area, the decrease in the influence of the parasympathetic link and the activation of the sympathetic part of the ANS on the heart rhythm in DLP and hypertension is explained by the probable development of left ventricular hypertrophy with the phenomena of cardiomyocyte desensitization in DLP in patients with CHF due to postinfarction cardiosclerosis. Diurnal HRV fluctuations are manifested by a large power of the LF spectrum with a simultaneous increase in the HF index. A uniform change in spectral frequencies leads to a slight shift in the LF/HF ratio towards increased activity of the sympathetic nervous system. These HRV changes in CHF with DLP may mask the existing disorders of neurohumoral regulation of the ANS [6,8].

In addition, another theory of the pathogenesis of increased activity of the sympathetic nervous system in DLP has recently been discussed, according to which the activation of SNS is due to an increase in the level of leptin in these patients. Leptin is a hormone synthesized by adipocytes of visceral adipose tissue, and its level is closely correlated with body mass index (BMI) and obesity. Leptin regulates the feeling of satiety at the level of the arched nucleus of the hypothalamus, which is closely related to the paraventricular nucleus, the stimulation of which leads to the activation of the sympathetic nervous system. It should be borne in mind that with dyslipidemia, which is present in patients with metabolic syndrome, atherosclerotic changes in the renal arteries may occur,

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leading to the development of renovascular hypertension and activation of the sympathoadrenal system [4,7].

The presented HRV changes in group 3 patients with CHF and MS are explained by the influence of increased body weight, diabetes mellitus on HRV parameters. Under the influence of insulin, there is an increase in the production of vasoconstrictor biologically active substances by the endothelium – endothelin, thromboxane A2 and a decrease in the secretion of such powerful vasodilators as prostacyclin and nitric oxide. Under the influence of the latter, it leads to an imbalance of the ANS.

Thus, according to some researchers, body weight, blood glucose and hypercholesterolemia also affect HRV parameters. At the same time, a lower body weight is manifested by a higher power of the HRV and HF spectrum, and in obese people, an inverse relationship is noted. There is a decrease in the power of all-time indicators of HRV [2,6,8]. In patients with CHF and DLP, there is a significant decrease in HRV indicators towards the predominance of sympathetic regulation over parasympathetic [4.10]. The greatest tension of regulatory systems was detected in patients with CHF and DM2, which may indicate a high risk of mortality in this group of patients.

Conclusions: In the 2nd group of patients with CHF and MS, in combination of which dyslipidemia is noted, it was revealed that along with a decrease in HRV, there is a decrease in the vagal effects of ANS (pNN50, RMSSD, HF). A decrease in the total HRV capacity in patients of the 2nd group of the study was accompanied by high indicators of sympathetic effects of ANS (SDANN, LF, LF/HF). According to studies in this area, the decrease in the influence of the parasympathetic and the activation of the sympathetic part of the ANS on the heart rhythm in DLP and hypertension is explained by the probable development of left ventricular hypertrophy with the phenomena of cardiomyocyte desensitization in DLP in patients with CHF due to postinfarction cardiosclerosis. Diurnal HRV fluctuations are manifested by a large power of the LF spectrum with a simultaneous increase in the HF index. A uniform change in spectral frequencies leads to a slight shift in the LF/HF ratio towards increased activity of

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the sympathetic nervous system. These HRV changes in CHF with DLP may mask the existing disorders of neurohumoral regulation of the ANS [6,8].

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