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Heart rate variability in people with metabolic syndrome

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Abstract. Metabolic syndrome (MS) is characterized by disorders of carbohydrate and fat metabolism, which can lead to the development of cardiac autonomic neuropathy (CAN). Heart rate variability (HRV) analysis is used to assess the state of autonomic regulation. A decrease in HRV indicates unfavourable changes in autonomic regulation and the development of CAN. The purpose of this study was to compare HRV parameters in patients with metabolic syndrome and healthy individuals without signs of MS. We examined 74 patients with metabolic syndrome (mean age 54.4 ± 1.1 years) and 61 healthy subjects (without signs of MS) (mean age 57.0 ± 1.6 years). The results of the study indicate a significant decrease in HRV in people with MS. However, they had significantly lower values of the SDNN index (by 26%), which characterizes the overall power of neurohumoral regulation of heart rate. Differences in the indicators characterizing short-term, vagal influences were especially pronounced: in patients with MS, RMSSD (by 44%) and HF (by 69%) were lower than in controls. The activity of the baroreflex center of the medulla oblongata, assessed by the spectral power of low-frequency waves (LF), was 55% lower in patients with MS compared to controls. There were no significant differences in the mean duration of the R-R interval, the spectral power of very low frequency (VLF) waves, or the ratio of the spectral powers of low and high frequencies (LF/HF, LFn, HFn) in patients with MS compared to controls. No significant shift in the autonomic balance towards sympathicotonia was found in patients with MS. The analysis of variance confirmed the significant effect of the metabolic syndrome factor on HRV. Thus, the data obtained indicate the development of CAN in people with metabolic syndrome, which is an unfavourable prognostic sign. To assess the effect of MS on the rate of aging, the biological age (BA) of the examined people with MS was calculated. The formula for calculating BA was obtained on a group of people without MS. The method of multiple stepwise regression was used. The aging rate was calculated as the difference between biological and chronological age (CA). The average BA in the group of people with MS was 63,20 ± 1,81 years, in the control group – 53.99 ± 1.71 years ($p< 0.05$). The difference between BA and CA is 8,81 ± 0,94 years in the group of people with MS and -1.01 ± 0.61 in control group ($p< 0.05$). From this we can conclude that MS can be a factor accelerating aging.

Keywords: metabolic syndrome, heart rate variability, biological age

Heart rate variability (HRV) is a generally accepted global standard for assessing the state of autonomic regulation of the heart [19, 20,]. A decrease in HRV indicates unfavourable changes in autonomic regulation and the development of cardiac autonomic neuropathy (CAN) [1, 15]. CAN is the main complication of type 1 and type 2 diabetes mellitus [1]. Diabetic CAN is defined by the Toronto Consensus Group as "impaired autonomic control of the cardiovascular system in the setting of diabetes after exclusion of other causes" [1, 2]. Many epidemiologic studies have shown an increase in morbidity, cardiovascular and overall mortality associated with CAN. However, CAN is increasingly being reported in people with prediabetes and metabolic syndrome (MS) with a prevalence of up to 11% and 24%, respectively.

CAN is associated with components of MS, in particular with hypertension and obesity, and precedes hyperglycemia. The aetiology of CAN is multifactorial, and there is a relationship between insulin resistance and metabolic syndrome. Obstructive sleep apnea is also associated with CAN, possibly through MS and an independent mechanism. Experts estimate that by 2045, the global prevalence of impaired glucose tolerance in the form of prediabetes will reach 587 million people, which means that CAN will become a significant clinical problem [4, 5, 6, 7]. CAN is independently associated with silent myocardial ischemia, major cardiovascular events, myocardial dysfunction, and cardiovascular mortality [1]. The consequence of CAN is the development of pathology of sympathetic and parasympathetic nerve fibres that innervate the heart and blood vessels [8]. Since neuropathy occurs in the longest nerve fibres, the earliest manifestations of autonomic neuropathy in diabetes mellitus are the result of denervation of the parasympathetic nervous system and changes in heart rate variability (HRV) [9, 10].

Early screening for the detection of CAN in people with prediabetes is carried out by analyzing heart rate variability (HRV) or by analyzing the skin-galvanic response, which is very important to ensure earlier initiation of treatment in the reverse stage of the disease [1]. In the later stages of CAN, disturbances in vascular tone and autonomic control of the heart rate develop, accompanied by tachycardia at rest, which eventually leads to a failure of normal blood pressure regulation, causing presyncope symptoms, exercise intolerance, palpitations, and fainting. These symptoms cause disability and impair quality of life [120]. They reflect the cardiovascular instability of severe CAN and the associated high risk of cardiovascular mortality [4]. Individuals with CAN and diabetes mellitus have a high incidence of sudden cardiac death [8]. CAN is an independent risk factor for an increased incidence of silent myocardial ischemia, major cardiovascular events, myocardial dysfunction, and cardiovascular mortality [2, 133].

Back in 1991, Ewing et al. showed that the resting QT interval, adjusted for heart rate (QTc), correlated with the stage of development of CAN in patients with diabetes. The study also showed that the resting QTc was the longest in individuals who died unexpectedly during follow-up, possibly due to cardiac arrhythmias [144]. In 2010, the ACCORD study showed that patients with type 2 diabetes mellitus who were diagnosed with CAN at the beginning of the study had a relative risk of mortality of 1.55-2.14 compared to those without CAN [11]. CAN is associated with a higher prevalence and more severe form of heart failure with preserved ejection fraction in patients with diabetes, with significant associated mortality [166, 177]. Yadav R.L. et al. (2017) showed that the recent increase in the prevalence of cardiovascular disease in people with obesity and normal glucose tolerance was associated with metabolic syndrome and autonomic dysfunction [18].

The association between obesity and CAN emphasizes the importance of lifestyle modification, including diet and physical activity, to counteract the development of MS and prevent the progression of CAN. Weight loss achieved through such lifestyle modifications, diet and exercise improves the functional activity of the sympathetic and parasympathetic parts of the heart rhythm regulation [1]. Honzikova N. showed that in elderly people with impaired carbohydrate tolerance, the power of the high-frequency component (HF) significantly decreases, which reflects a predominant decrease in parasympathetic effects on the cardiovascular system [19]. They also have a higher LF/HF ratio, which characterizes a relative increase in sympathetic activity in patients of this group. These changes are characteristic of the state of stress and adversely affect the cardiovascular system, which can lead to myocardial ischemia, hypertension, and reduced carbohydrate tolerance. Malik M. and Camm A.J. (1993) in their studies draw attention to the fact that heart rate variability characterizes the fluctuations in the

effects of the autonomic nervous system (ANS) on the heart, rather than the average level of the ANS state. Therefore, both the blockade of the effects of the ANS and an excessively high level of sympathetic stimulation leads to a decrease in HRV [20]. Thus, the assessment of heart rate variability is an important component of the diagnosis of the severity of the metabolic syndrome and associated cardiac autonomic neuropathy.

This study aimed to compare HRV indices in individuals with metabolic syndrome and healthy individuals without signs of MS

Materials and methods

We examined 74 patients with metabolic syndrome (mean age 54.4±1.1 years) and 61 healthy individuals (without signs of MS) (mean age 55.0±1.6 years). The diagnosis of metabolic syndrome and insulin resistance was based on the results of laboratory diagnostics, which included the determination of the following markers of MS: glycosylated haemoglobin (HbA1c), insulin, fasting glucose level >110 mg/dL (6.1 mmol/L), HOMA index, lipid profile (HDL-C, TG >150 mg/dL (1.69 mmol/L), VLDL-C, HDL-C <50 mg/dL (1.04 mmol/L), VLDL-C) and atherogenicity coefficient. Anthropometric parameters were assessed in all patients: body weight, height, body mass index (BMI), waist circumference (> 88 cm), and hip circumference. For the diagnosis of overweight and obesity, BMI or the Ketle index was used, which was calculated according to the ratio of body weight to height squared (kg/m2). According to WHO (1997), BMI in the range of 20 to 24.9 kg/m2 was considered normal body weight, BMI from 25 to 29.9 kg/m2 was assessed as overweight, BMI from 30.0 to 34.9 kg/m2 was considered obesity (grade I), BMI from 35.0 to 39.0 kg/m2 was considered severe obesity (grade II), and BMI more than 39.0 kg/m2 was considered very severe obesity (grade III). Blood pressure was measured in both arms at rest to determine the presence of signs of hypertension (>130/85 mm Hg). All subjects were instructed to avoid alcohol or caffeinated drinks after 10:00 pm. (22:00) the night before the examination. In addition, they refrained from smoking 1 hour before the measurement. ECG measurements were taken from 10:00 to noon, in the supine positions (at 5 minutes). During the ECG recording, the subject was instructed to breathe according to his/her normal rate. 12-lead ECG registration was carried out using the ECG-recorder DiaCard (Solvaig, Ukraine). ECG and HRV analysis were performed by DiaCard ECG-recorder v. 1.0.0.73. HRV scores were calculated in the time domain and frequency-domain:

SDNN – the standard deviation of NN intervals; variance of all NN intervals.
RMSSD – the square root of the mean of the squares of the successive differences between adjacent NNs;
parasympathetic activity.
pNN50 – the proportion of pairs of successive NNs that differ by more than 50 ms; parasympathetic activity.
TP –total power (≤ 0.40 Hz); variance of all NN intervals.
VLF – power in a very low-frequency range (0.003-0.040 Hz); humoral influences.
LF – power in the low-frequency range (0.040-0.150 Гц); sympathetic and vagal influences.
HF – power in the high-frequency range (0.150-0.400 Hz); parasympathetic activity.
LF/HF – Sympathetic-vagal index.

Note: the term "NN" is used in place of RR-interval ECG to emphasize the fact that the processed beats are "normal" beats.

To analyze the data obtained we used Statistica 7.0 (StatSoft, USA). The significance of differences in mean values was assessed by Student's T-test. One-factor analysis of variance (ANOVA) was used to evaluate the differences in HRV in patients with MS and control subjects (without signs of MS). The factor, in this case, was the presence or absence of metabolic syndrome.

Results and discussion

The results of the HRV analysis in the studied persons, depending on the presence of metabolic syndrome, are shown in Table and Figure.

Table

Average values of HRV indices in people with metabolic syndrome (MS) and in the group of people without MS

HRV indicators	Persons without MS, n=61, M ± m	Persons with MS, n=74, M ± m
NN, ms	902 ± 19	878 ± 14
Ln NN	6.79 ± 0.03	6.77 ± 0.02
SDNN, ms	45.7 ± 3.7	33.9 ± 1.7**
Ln SDNN	3.65 ± 0.07	3.45 ± 0.05*
RMSSD, ms	44.3 ± 5.4	24.8 ± 1.5***
Ln RMSSD	3.44 ± 0.10	3,.07 ± 0.06**
pNN50,%	9.24 ± 1.74	5.37 ± 1.05
TP, ms^2	2508 ± 439	1260 ± 153**
Ln TP	7.20 ± 0.14	6.82 ± 0.09*
VLF, ms^2	722 ± 131	593 ± 87
Ln VLF	6.08 ± 0.13	6.02 ± 0.09
LF, ms^2	816 ± 207	367 ± 51*
Ln LF	5.84 ± 0.16	5.47 ± 0.10
HF, ms^2	970 ± 225	304 ± 36**
Ln HF	5.81 ± 0.19	5.22 ± 0.12*
LF/HF	1.53 ± 0.20	1.79 ± 0.21
Ln LF/HF	0.03 ± 0.12	0.24 ± 0.10
LFn, %	50.6 ± 2.4	55.2 ± 2.1
HFn, %	49.2 ± 2.5	44.8 ± 2.1

Notes: * - the probability of differences in average values at the level of $p < 0.05$;
** - the probability of differences in average values at the level of $p < 0.01$;
*** - the probability of differences in average values at the level of $p < 0.001$.

As can be seen from the data presented in table 1, in people with MS there were no significant differences with the control in the value of the average duration of the R-R interval (NN), the spectral power of very low-frequency waves (VLF, Ln VLF), the ratio of the spectral powers of low and high frequencies (LF/HF, Ln LF/HF, LFn, HFn). However, they showed significantly lower values of SDNN (by 26%), Ln SDNN, TP (by 50%), and Ln TP, which characterize the total power of neurohumoral regulation of heart rate. The differences in the indicators characterizing short-term, vagal influences were especially pronounced: in patients with MS, RMSSD (by 44%), Ln RMSSD, HF (by 69%), and Ln HF was lower than in controls. The activity of the baroreflex centre of the medulla oblongata, assessed by the spectral power of low-frequency waves (LF), in people with MS was 55% lower compared to controls. A study of patients with metabolic syndrome showed changes in autonomic regulation of heart rate similar to those described in studies by other authors [1, 188], namely, a decrease in the activity of vagal modulation of heart rate, the activity of the baroreflex centre of the medulla oblongata, and a decrease in the total HRV. At the same time, the activity of the regulatory effect on the heart rate from the subcortical sympathetic ergotropic centres in individuals with MS did not differ from the control group. At this stage of our research, probably due to the insufficiently large sample size, no significant shift in the autonomic balance towards sympathicotonia was found in patients with MS, according to the LF/HF ratio. The use of logarithmic HRV values, which are usually used to reduce within-group variance, did not lead to an increase in the degree of significance of differences between the mean values of the two groups compared.

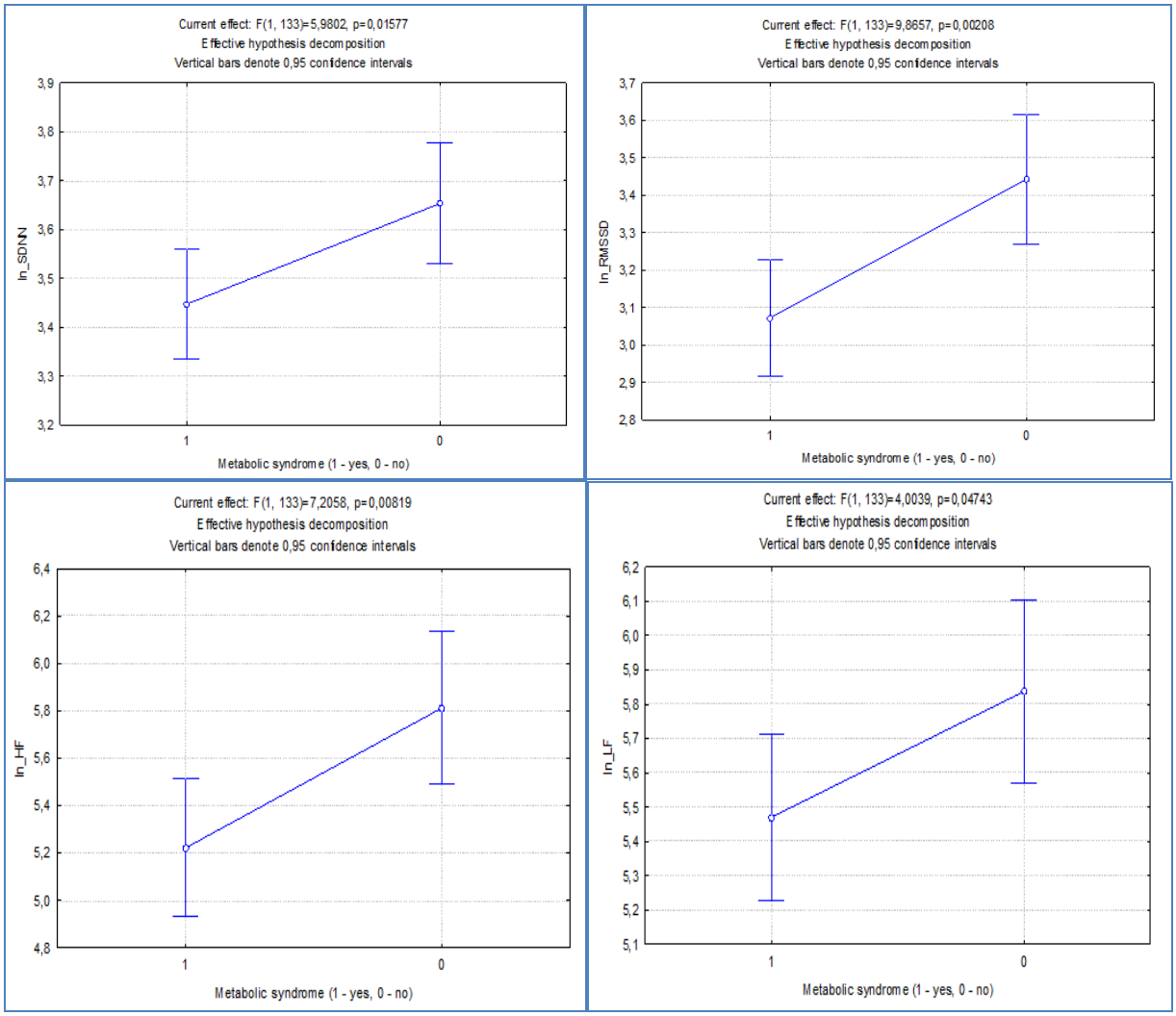

Figure. The validity of the influence of the presence of the metabolic syndrome factor on heart rate variability indicators (ANOVA).

To assess the reliability of the influence of the factor of the presence of metabolic syndrome in individuals, one-factor analysis of variance (ANOVA) was performed. According to the data obtained (Figure), this factor has a significant effect on the main HRV parameters.Thus, the data obtained indicate the development of CAN in people with metabolic syndrome, which is an unfavourable prognostic sign.

To assess the effect of MS on the rate of aging, the biological age (BA) of the examined people with MS was calculated. The formula for calculating BA was obtained on a group of people without MS. The method of multiple stepwise regression was used. The aging rate was calculated as the difference between biological and chronological age (CA).

Biological age was calculated using the formula:

$$BA\ (years) = 40.91 - 0.887\ SDNN\ (ms) + 0.0185\ VLF\ (ms^2) + 0.761\ CA\ (years)$$

The average BA in the group of people with MS was 63.2 ± 1.81 years, in the control group – 53.99 ± 1.71 years ($p < 0.05$). The difference between BA and CA is 8.81 ± 0.94 years in the group of people with MS and -1.01 ± 0.61 in control group ($p < 0.05$). From this we can conclude that MS can be a factor accelerating aging.

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