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Dynamics of features of heart rate variability with application of alpha-lipoic acid in patients with type 2 diabetes mellitus who have had myocardial infarction

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Abstract
The article presents the dynamics of heart rate variability (HRV) features of 59 patients with type 2 diabetes mellitus (DM) who have had non-Q-myocardial infarction (non-Q-MI) under the influence of 4-month treatment of alfa-lipoic acid (ALA). Treatment showed a significant increase in high frequency activity HF ($p<0.01$), HFnorm ($p<0.05$) in the daytime with an increase in its contribution to the total spectral power – HF% ($p<0.05$). Besides, it was recorded a decrease in percentage contribution of low-frequency LFnorm% ($p<0.001$) and the growth of high-frequency HFnorm% activity ($p<0.001$) in the autonomic regulation of heart rate during the active period of time, which is reflected in sympathovagal interaction index LF/HF ($p<0.001$). Thus, the 4-month use of ALA in addition to the basic therapy of patients with type 2 DM who had non-Q-MI, causes positive effect on HRV, that includes the increase in the tone of the parasympathetic link of autonomic nervous system and normalizing of sympathovagal interaction in daytime.

Keywords: Heart rate variability, type 2 diabetes mellitus, non-Q-myocardial infarction, alpha-lipoic acid

1. Introduction

A sensitive criterion of evaluation of the influences of the autonomic nervous system on the heart is heart rate variability (HRV). In patients with ischemic heart disease, particularly in post-infarction patients, HRV decreases significantly with the weakening of parasympathetic influences on the heart and impaired sensitivity of baroreceptors, what causes the increase in sympathetic activity [1, 2]. It is known that the decrease of HRV is an unfavorable factor in the occurrence of arrhythmias, including vitally threatening arrhythmia, it increases the risk of sudden cardiac death (SCD). There is evidence that low HRV indices are correlated with a risk of SCD even more than ejection fraction, category of ventricular arrhythmias and physical tolerance [3, 4]. The decreasing of the HRV in diabetics is an indicator of the cardiac autonomic neuropathy (CAN) and it's regarded as a predictor of cardiovascular morbidity and mortality [5, 6].
Especially vulnerable are the patients with diabetes mellitus (DM) who have had myocardial infarction (MI), via summation of negative influences on the autonomic regulation of cardiac activity, which increases the electrical instability of the myocardium.

As oxidative stress plays the dominant role in the development and progression of the most chronic complications of diabetes, including CAN, the decrease in the activity of the process of peroxidation may be an effective strategy to impact on violations of HRV [7, 8].

The purpose of the study is to investigate changes in heart rate variability (HRV) features in patients with type 2 DM who have had non-Q-myocardial infarction (non-Q-MI) under the influence of alpha-lipoic acid (ALA).

2. Materials and methods

59 patients were examined (36 men and 23 women, mean age 62,09 ± 1,32 years) with type 2 DM who have had non-Q-MI. The patients' baseline characteristics are summarized in Table 1.

Patients were included in the study if they met the following criteria: 1) type 2 DM treated with oral antidiabetic drugs; 2) history of non-Q-MI; 3) signed informed consent for participation in the study.

Patients were excluded from the study according to the following criteria: 1) the patient has type 1 DM; 2) congenital and acquired heart defects; 3) atrial fibrillation / flutter; 4) secondary AH; 5) heart failure (NYHA class III-IV); 6) liver and kidney diseases.

At the time of the study, the patients received basic therapy: ACE inhibitor, β-blocker, statin,

Table 1: Baseline characteristics of the studied patients.

Characteristics		Studied patients (n=59)
Age, M±m years		62,09±1,32
Sex: (n, %)	Male	36 (61,0%)
	Female	23 (39,0%)
Time after non-Q-MI, M±m years		4,55±0,59
DM duration, M±m years		7,92±0,54
FG, mmol/L		9,09±0,42
HbA1c, %		7,77±0,20
HOMA-IR		6,99±0,71
TC, mmol/L		5,52±0,15
TG, mmol/L		2,66±0,19
LDL-C, mmol/L		3,39±0,13
HDL-C, mmol/L		0,97±0,03
Grade 1-2 hypertension (n, %)		45 (76,3%)
Office SBP, M±m mm Hg		140,11±2,02
Office DBP, M±m mm Hg		86,84±1,83

FG – fasting glucose, HbA1c – glycated hemoglobin level, HOMA-IR – the homeostasis model assessment of insulin resistance, TC – total cholesterol, TG – triglyceride, LDL-C – low-density lipoprotein cholesterol, HDL-C – high-density lipoprotein cholesterol, SBP – systolic BP, DBP – diastolic BP.

antiplatelet agent, oral hypoglycemic therapy. For the basic treatment of patients it was added ALA 600mg/day. The duration of treatment and monitoring of patients was 4 months.

All participants before taking ALA and at the end of the treatment underwent 24-hour ECG (Holter) monitoring using a device "Cardiosens K" (Ukraine, 2010). 24-hour ECG monitoring was conducted ambulatory in the free movement regime of the patient.

HRV was measured by computerized analysis of long term heart rate samples with a 24-hour Holter monitoring. Several temporal and spectral indexes of HRV were evaluated. In particular, the time domain parameters: mRR (ms) – average R-R interval of the sinus rhythm; SDNNi (ms) – standard deviation of all normal R-R intervals for all 5-min segments; RMSSD (ms) – square root of the mean squared difference of successive R-R intervals. In addition, it was analized the index pNN50% – proportion of successive R-R intervals that differ by more than 50 ms. The following components of the spectral analysis of HRV were determined: HF (High Frequency, ms^2) – high-frequency component (0.15–0.4 Hz), a variability

modulated by the parasympathetic system; LF (Low Frequency, ms^2) – low-frequency component (0.04–0.15 Hz), modulated by the sympathetic system and VLF (Very Low Frequency, ms^2) – very low frequency component (0.003 to 0.04 Hz), associated with humoral-metabolic regulation mechanisms. Total spectral power (TP-Total Power, $мс^2$) at the whole range of frequencies (0.003–0.15 Hz) was analyzed. HF, LF power presented both in absolute units and in normalized – HFnorm and LFnorm, which were obtained by calculation: LF or HF / (TP – VLF)*100, which allowed to exclude the effect of VLF component. HFnorm% and LFnorm% – relative indicators reflecting the contribution of the spectral components in autonomic regulation. Calculated low-frequency to high-frequency component ratio (LF/HF) that indicated the balance of sympathetic and parasympathetic nervous modulation. HF%, LF% and VLF% – relative indicators reflecting the contribution of each spectral component in the spectrum of neurohumoral regulation.

The protocol of the study was approved by the Ethics Committee of the O.O. Bogomolets National Medical University. All patients gave their informed written consent to participate in the study.

Statistical processing of the study results was conducted using parametric methods. The accuracy of differences in comparing mean values before and after treatment was determined using Student's *t*-test. Value of $p<0,05$ was considered to be significant. The value of studied parameters are presented as M±m, where m – arithmetic mean value, m – standard error. Statistical analysis was performed by Statistics Package for Social Science (SPSS version 13.0, SPSS Inc., USA).

3. Results and their discussion

According to our previous data [9], the HRV indices in the examined post-infarction patients with type 2 diabetes mellitus were characterized by a decrease of neurohumoral regulation of the cardiac activity with the weakening of both the sympathetic and parasympathetic and also humoral-metabolic influences on the cardiac rhythm. In addition, it was observed disbalance of the autonomic nervous system with predominance of sympathetic over parasympathetic regulation.

Analyzing the temporal indexes of HRV in patients with type 2 DM who have had non-Q-MI after 4 months of application of ALA it was found a tendency to increase daytime RMSSD ($p<0,2$) and pNN50% ($p<0,2$), that indicates the growing contribution of the parasympathetic autonomic nervous system in regulation of heart rate during the active period of time (tabl. 2.).

Table 2: Temporal indexes of HRV in the studied patients before and after treatment (M±m).

Parameters, units	Time of determining	Studied patients (n=59)	
		Day	Night
mRR, ms	1	854,19±14,00	947,87±13,01
	2	836,00±18,14	927,74±17,97
SDNNi, ms	1	41,65±1,89	44,50±2,03
	2	42,39±1,76	45,15±2,40
RMSSD, ms	1	21,52±1,58	27,87±2,55
	2	24,99±1,95	30,80±2,03
pNN 50, %	1	2,97±0,59	6,48±1,20
	2	4,63±1,10	7,66±1,09

1 – before treatment, 2 – after 4 months of treatment.

So, the results of the study indicate positive trends in autonomic regulation of cardiac activity as for the patients studied during therapy.

Whereas the temporal indexes give only a general approximate characteristics of the HRV, for a more detailed assessment of the effectiveness of the applied treatment the spectral parameters of HRV were analyzed (tabl. 3.).

Table 3: Spectral indexes of HRV in the studied patients before and after treatment (M±m).

Parameters, units	Time of determining	Studied patients (n=59)	
		Day	Night
TP, мс^2	1	1848,45±164,70	2128,55±172,89
	2	1942,68±154,52	2159,87±170,15
VLF, мс^2	1	814,68±70,17	979,97±77,18
	2	802,10±65,33	973,58±78,58
VLF, %	1	44,46±0,81	46,93±1,32
	2	41,81±1,07	45,63±0,87
LF, мс^2	1	273,45±25,83	432,77±39,92
	2	318,29±30,24	461,55±39,96
LF, %	1	15,00±0,81	20,01±0,81
	2	15,98±0,80	20,86±0,72
HF, мс^2	1	124,84±17,20	254,32±46,98
	2	197,23±22,09**	280,35±35,81
HF, %	1	6,84±0,85	10,85±1,43
	2	10,22±1,11*	12,43±1,04
LFnorm	1	27,15±1,49	37,89±1,48
	2	27,45±1,27	38,35±1,19
LFnorm, %	1	71,05±1,71	67,51±2,26
	2	63,08±1,78***	63,83±1,99
HFnorm	1	12,34±1,52	19,84±2,18
	2	17,21±1,68*	22,61±1,72
HFnorm, %	1	28,95±1,71	32,50±2,26
	2	36,92±1,78***	36,17±1,99
LF/HF	1	2,87±0,26	2,50±0,22
	2	1,93±0,16***	2,06±0,19

1 – before treatment, 2 – after 4 months of treatment; * – $p<0{,}05$, ** – $p<0{,}01$, *** – $p<0{,}001$ compared with data before treatment.

On the background of the treatment of patients it was observed a significant increase in high frequency activity HF ($p<0.01$), HFnorm ($p<0.05$) in the daytime with an increase in its contribution to the total spectral power HF% ($p<0.05$), which confirms the growing role of the parasympathetic link of autonomic nervous system in the regulation of cardiac rhythm in these patients.

It was also observed a decrease in percentage contribution of low-frequency LFnorm% ($p<0.001$) and the growth of high-frequency HFnorm% activity ($p<0.001$) in the autonomic regulation of heart rate during the active period of time, which was reflected in sympathovagal interaction index LF/HF ($p<0.001$). In addition, it was registered a tendency towards an increase of sympathetic influences – LF ($p<0.2$) and a decrease in the percentage contribution of humoral-metabolic regulation mechanisms – VLF% ($p<0.2$). It was not recorded any significant changes in the HRV indices during nighttime, however, positive trends were observed in the settlement participation of the branches of autonomic regulation with increase of parasympathetic involvement HFnorm ($p<0.2$), HFnorm% ($p<0.2$) and decrease in sympathetic influences LFnorm% ($p<0.2$), which reduced the ratio of sympatho-vagal activity LF/HF ($p<0.2$).

Consequently, the use of ALA in addition to the basic therapy in studied patients resulted in the activation of parasympathetic link of autonomic nervous system and reduced sympathetic influences in daytime, whereas night indicators had only a positive tendency to changes.

According to the literature data we have analyzed existing information regarding the effect of ALA on parameters of HRV.

Numerous studies have proven the efficacy of ALA in treating diabetic peripheral neuropathy. There is less information regarding its use in CAN. The most important researches in this direction is the DEKAN [10] and NATAN-1 [11], in which ALA has shown its effectiveness in the treatment of diabetic CAN, leading to significant improvement of HRV. Herewith, the doses and duration of treatment differed. Thus, the study DEKAN provided for the reception of ALA in a dose of 800mg/day for 4 months, while NATAN-1 – 600мг/day with prolonged duration of treatment up to 4 years. The results of these studies are consistent with our data.

In contrast to the presented results in the randomized, parallel, placebo-controlled study [12] with the use of combined antioxidant therapy in patients with type 1 diabetes mellitus, that included allopurinol (300 mg daily), ALA (600 mg twice daily) and nicotinamide (750 mg twice daily), it wasn't recorded the prevention of the progression of CAN. The duration of treatment was 24 months. This study makes it impossible to clearly assess the effect of ALA, because the drug was used in the combined treatment.

Thus, the presented clinical data of studies on the efficacy of ALA in diabetic CAN shows conflicting results although most of them testify to its effectiveness in the correction of HRV features, which is also confirmed by the results of our study. More studies in larger patient populations are needed to clarify ALA effects on HRV.

4. Conclusion

The use of ALA for 4 months in patients with type 2 DM who had non-Q-MI, causes positive effect on HRV, that includes the increase in the tone of the parasympathetic link of autonomic nervous system and normalizing of sympathovagal interaction in daytime.

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