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MODULATION OF HEART RATE VARIABILITY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS ASSOCIATED WITH CAROTID ATHEROSCLEROSIS

Sadomov A.S., Nasonenko O.V.
Zaporizhzhia State Medical University

Heart rate variability (HRV) is a proven predictor of cardiovascular events in the general population, and especially in patients with type 2 diabetes mellitus (T2DM). Early detection of autonomic dysfunction in T2DM can help to detect the developing atherosclerosis in earlier stages to prevent unfavorable outcomes. This study evaluates the impact of T2DM associated with carotid atherosclerosis on HRV parameters.
Keywords: type 2 diabetes mellitus, carotid atherosclerosis, heart rate variability, cardiovascular events, carotid intima-media thickness.

Heart rate variability (HRV) is definitely one of main proven predictors of cardiovascular mortality.

HRV is a noninvasive tool to assess autonomic function. The Atherosclerosis Risk in Communities study has shown reduced HRV as an independent factor of increased value of cardiovascular events, especially of coronary artery disease [2; 3]. It is known that the dysregulation of the autonomic function is associated with increased risk of cardiac death in patients with diabetes and hypertension, as well as with poor prognosis of cardiovascular events [1]. Type 2 diabetes mellitus is associated with a higher risk of atherosclerosis that is known as a sensitive marker of cardiac morbidity and mortality. Due to limitations Framingham Risk Score because of low sensitivity and specificity additional markers, such as HRV changes, may be useful in prevention and early diagnosis of cardiovascular (CV) complications in general population.

The objective was to assess changes of HRV parameters depending on presence or absence of stenotic lesions of brachiocephalic arteries in patients with diabetes mellitus type 2 (T2DM).

Materials and methods. 43 patients with T2DM and 15 non-diabetic healthy control subjects were involved into this study. All participants were matched for sex and age (32 men and 26 women, mean age 53±6,3 years). Subjects with previous history of CV events, such as the myocardial infarction or stroke, were excluded. All included participants were subjected to color duplex scanning of brachiocephalic arteries with measurement of carotid intima-media thickness (CIMT). HRV assessment was performed for all subjects according to the guidelines of the Task Force for Pacing and Electrophysiology [3]. Patients thus followed the usual daily regimen. The duration of monitoring was 24 hours. Calculation of heart rate variability was performed considering of successive R-R intervals of sinus origin for duration of 300 s with a pitch of 1 min and calculation of standard time parameters in day and night periods. Spectral analysis was performed using the method of fast Fourier transformation with calculation of power spectral density in the following frequency bands: very low frequency (VLF) – 0,0033-0,04 Hz, low frequency (LF) – 0,04-0,15 Hz, high frequency (HF) – 0,15-0,4 Hz. Total power spectrum (TS) and the ratio of low-to high-frequency component (LF / HF), the value of low-power and high-frequency components of the spectrum, expressed in normalized units (LFnorm%, HFnorm%) were also calculated. Indicators were measured automatically every five minutes of recording. Five-minute intervals, which included non-stationary processes, artifacts and frequent premature ventricular beats were excluded from the calculation by direct analysis of the record. We analyzed the records of length not less than 18 hours, which included overnight. To investigate the circadian fluctuations in HRV all studied parameters were calculated in active (from 7:00 AM to 10:00 pm) and passive (from 12:00 PM to 6:00 AM) periods of the day. Circadian index was also calculated for all records. It was performed also laboratory testing, that included the measurement of fasting plasma glucose (FPG), total cholesterol, triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL). All patients were fasted more than 10 hours before drawing of blood samples.

Results. Table 1 summarizes the general characteristics of study groups. Mean duration of T2DM was 6,4±3,7 years for diabetic group. Systolic

Table 1

General characteristic of study groups

	Participants with T2DM, n=43 Mean value±standart deviation	Non-diabetic subjects, n=15 Mean value±standart deviation
Age	54±5,2	51±6,3
Sex: male%	56	53
T2DM duration	6,4±3,7	-
FPG, mmol/l	8,8±3,6	4,2±1,9
Total cholesterol, mmol/l	5,3±2,8	4,3±0,9
LDL cholesterol, mmol/l	4,8±0,7	3,3±0,8
HDL cholesterol, mmol/l	1,1±0,2	1,5±0,4
CIMT, mm: left/right	0,77±0,06/0,76±0,07	1,18±0,05* /1,07±0,04*
Total cases of carotid stenotic lesions	28	0
The average volumetric flow velocity of the common carotid arteries Vvol med, ml/min	538,2±46,8	483,7±51,1*

*Note: * – p≤0,05 compared to control group*

blood pressure was significantly higher in patients with longer history of T2DM and had a direct association with state of compensation T2DM. The FPG, LDL, total cholesterol levels were significantly higher in diabetic group compared to non-diabetic subjects ($p \leq 0,05$). By ultrasound dopplerography in 65,1% of patients with T2DM were found early signs of non-stenotic carotid atherosclerosis and stenotic carotid lesions, while the control group had any evidence of atherosclerosis of brachiocephalic arteries (BCA). In 13% of stenosis cases observed bilateral lesions of BCA. Structural vascular atherosclerotic pathology in subject from control group was not found in 100% cases, all arteries remained intact. The development of atherosclerosis is closely linked to the activation of compensatory-adaptive mechanisms of redistribution of blood flow, which manifests as the formation of hyperkinetic haemodynamics variant with decreased volumetric blood flow velocity in all basins.

Table 2 shows the HRV parameters measured in participants of both groups. Analysis of HRV showed a significant reduction of average time values of HRV in patients with T2DM compared with those of healthy people. These changes are particularly clear for SDNN. It is equivalent by the physiological meaning to the TP, pNN50 and RMSSD, that in turn is a reflection of rapid high-frequency oscillations. According to the results it can be concluded dysfunction of autonomic control of heart rate in patients of both T2DM studied groups. More expressed reduction of total power of spectrum proved for patients with carotid atherosclerosis. Significant reduction of spectral power in HF band (expressed in normalized units) and in total power was also observed in T2DM participants relative to controls. It was found the high correlation between HF part of spectrum and total power in diabetic patients. Physiological fluctuations in TP, SDNN per day were seen in the control group by the analysis of circadian changes, and it was a logical increase of these at night. Improving of performance rMSSD, pNN50, HF with a decrease in LF / HF ratio seems as a display of dominance regulatory vagal activity, whereas active period of the observed increase in LF, LF%, LF / HF resulting of sympathetic hyperactivity.

The correlative analyses show that CIMT correlates with decreasing of time-domain and frequency-domain of spectrum. The most expressed reduction is observed for TP and SDNN and also relates to a violation of circadian activity of the autonomic nervous system.

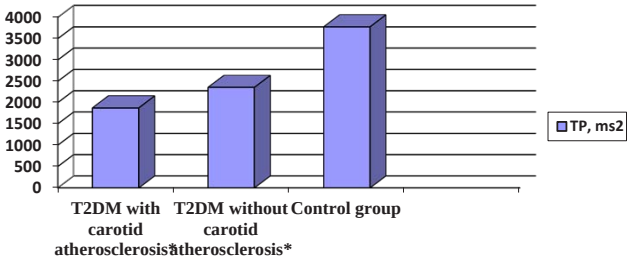

Fig. 1. Changes in the total spectral power in the study groups according to the presence or absence of atherosclerotic carotid arteries

*Note: * – p≤0,05 compared to control group*

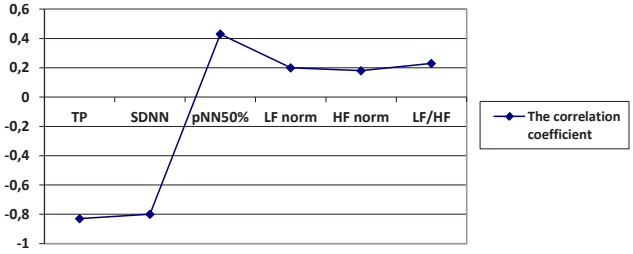

Fig. 2. Correlation between HRV parameters and CIMT in diabetic subjects

Discussion. The autonomic nervous system is often imbalanced in patients with type 2 diabetes mellitus and this neuropathy may be clinically unapparent. Heart rate variability is reduced in T2DM subjects, suggesting as a part of cardiac autonomic neuropathy as the complication of T2DM. The dysfunction of sympathetic branch of heart's autonomic regulation has been associated with increased risk for CV events and cardiac mortality. The significance findings is that HRV reduction in diabetics was present since the early stages of diabetes even before clinical atherosclerotic cardiovascular disease became evident. So, it is necessary to screen for autonomic neuropathy as early as possible in T2DM to identify and prevent the development of serious CV events.

Significantly reduced HRV in diabetic patients have been shown previously in many multicenter randomized studies [1; 5; 6]. The results showed lower SDNN, HF and LF part in T2DM opposed to non-diabetic subjects. A reduction in time-domain parameters of heart rate variability seems not only to

Table 2

HRV parameters in study groups

	Participants with T2DM, n=43 Mean value±standart deviation		Non-diabetic subjects, n=15 Mean value±standart deviation
	With carotid atherosclerosis, n=28	Without carotid atherosclerosis, n=15	
TP, ms^2	1876,85±72,8*	2358,92±116,27*	3778,52 ±229,32
SDNN, ms	131,16±6,51*	145,16±11,21*	155,15±21,84
RMSSD, ms	34,45±1,95	34,06±1,52	33,3±2,66
pNN50,%	14,6±0,95	12,48±1,44	12,87±1,90
LFnorm,%	43,16±2,0*	67,12±8,66*	29,9±2,21
HFnorm,%	20,27±0,92	27,17±2,85	18,98±1,42
LF/HF, standard units	2,12±0,05	2,83±0,13*	1,58±0,05
VLF, ms^2	725,93±12,56	1053,71±69,3	867,25±32,43
LF, ms^2	495,63±7,63*	995,06±21,22	868,9±20,13
HF, ms^2	232,93±7,51*	351,11±16,01	550,3±22,5
IC, standard units	2,61±0,14	5,84±0,36*	2,36±0,08
Heart rate, beats per min.	71,9±4,71	72±4,69	65,6±2,97

*Note: * – p≤0,05 compared to control group*

carry negative prognostic value but also to precede the clinical expression of autonomic neuropathy.

In addition, it was found the positive correlation between CIMT and value of HRV reduction for group with T2DM (picture 2). The maximal correlation was reported between CIMT and TP. Changing the TP and SDNN parameters shows strong reverse negative correlation with remodeling brachiocephalic vessels, which indicates an insufficient functional state of the autonomic control of heart rate. Except decreasing of frequency-domain parameters observed the violation of circadian activity and reduction of time-domain data according to both groups with T2DM. But circadian rhythm of HRV in patient with atherosclerosis characterized by further reducing of sympathetic and parasympathetic influences in active and passive hours. A low LF HRV may predict the progression of atherosclerosis in diabetic patients [7].

Conclusion. The reduction of HRV and its time-domain and frequency-domain parameters should be monitored even in early stage from the onset of T2DM, even if there are no symptoms of atherosclerotic lesions of carotid arteries, as a part of diagnostic the cardiac autonomic neuropathy. On the other hand, the concomitant history of carotid atherosclerosis is one more important factor of HRV reducing. This is considerable reason to perform 24-hour ECG recording for baseline evaluation in all patients with diabetes, along with ultrasound examination. The reasons are obvious, as is well known that lower HRV is associated with increased cardiovascular risk.

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Садомов А.С., Насоненко О.В.
Запорізький державний медичний університет

МОДУЛЯЦІЯ ВАРІАБЕЛЬНОСТІ СЕРЦЕВОГО РИТМУ У ХВОРИХ НА ЦУКРОВИЙ ДІАБЕТ 2 ТИПУ, АСОЦІЙОВАНИЙ ІЗ КАРОТИДНИМ АТЕРОСКЛЕРОЗОМ

Анотація
Варіабельність серцевого ритму (ВСР) є доведеним предиктором серцево-судинних подій як у загальній популяції, так, зокрема, і у пацієнтів з цукровим діабетом 2 типу (ЦД 2 типу). Раннє виявлення вегетативної дисфункції у хворих на ЦД 2 типу може сприяти діагностиці атеросклерозу на ранніх стадіях для профілактики несприятливих результатів надалі. У даному дослідженні оцінюється вплив ЦД 2 типу, пов'язаного з атеросклерозом сонних артерій, на зміну показників ВСР.
Ключові слова: цукровий діабет 2 типу, атеросклероз сонних артерій, варіабельність серцевого ритму, серцево-судинні події, товщина інтима-медіа сонних артерій.

Садомов А.С., Насоненко А.В.
Запорожский государственный медицинский университет

МОДУЛЯЦИЯ ВАРИАБЕЛЬНОСТИ СЕРДЕЧНОГО РИТМА У БОЛЬНЫХ САХАРНЫМ ДИАБЕТОМ 2 ТИПА, АССОЦИИРОВАННЫМ С КАРОТИДНЫМ АТЕРОСКЛЕРОЗОМ

Аннотация
Вариабельность сердечного ритма (ВСР) является доказанным предиктором сердечно-сосудистых событий как в общей популяции, так, в частности, и у пациентов с сахарным диабетом 2 типа (СД 2 типа). Раннее выявление вегетативной дисфункции у больных СД 2 типа может способствовать диагностике атеросклероза на ранних стадиях для профилактики неблагоприятных исходов в дальнейшем. В данном исследовании оценивается влияние СД 2 типа, ассоциированного с атеросклерозом сонных артерий, на изменение показателей ВСР.
Ключевые слова: сахарный диабет 2 типа, атеросклероз сонных артерий, вариабельность сердечного ритма, сердечно-сосудистые события, толщина комплекса интима-медиа сонных артерий.