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DEPENDENCE OF HEART RATE VARIABILITY ON INDICATORS OF TYPE 1 DIABETES MELLITUS CONTROL

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Ключевые слова: *сахарный диабет 1 типа, вариабельность сердечного ритма, показатели контроля*

Abstract. Dependence of heart rate variability on indicators of type 1 diabetes mellitus control. Pertseva N.O., Gurzhiy O.V., Moshenets K.I. *The aim of our study was to evaluate the influence of the main indicators of type 1 diabetes mellitus (T1DM) control on heart rate variability (HRV). We examined 62 patients at the age of 18-45 years with an average T1DM duration of 11.0 (5.0; 18.0) years. HRV in the time and frequency range was evaluated by analyzing a 24-hour Holter electrocardiogram (ECG). The following laboratory parameters were used as markers of course and compensation of T1DM: C-peptide, HbA1c, blood creatinine, albuminuria (AU), estimated glomerular filtration rate (eGFR) by CKD-EPI formula. In addition, the maximum and minimum blood glucose levels and the blood glucose range (maximum minus minimum blood glucose values) were conducted by continuous glucose monitoring system iPro2 (Medtronic MiniMed, USA). The daily monitoring of electrocardiogram (ECG) was made in parallel with long term monitoring of blood glucose. Echocardiography in all patients was performed to exclude organic heart disease and the possibility of its influence on HRV. Poor control of T1DM negatively influences HRV through decrease in both frequency and time characteristics. The blood glucose range can be an additional negative factor for cardiovascular system in T1DM patients, regardless of HbA1c, whereas it positively correlates with HRV – relative hypersympathicotonia markers: LF/HF 24-h, $\rho=0.43$ ($p<0.05$), LF/HF day $\rho=0.37$ ($p<0.05$), $\rho=0.38$ LF/HF night. Diabetic nephropathy is another factor of cardiovascular disease progression in T1DM, since its criteria have reliably negative (for eGFR) and positive (for AU) correlations of mean force with all HRV characteristics. Selected markers of T1DM control cause 45.73% of variance in HRV, mainly affecting TP 24-h, TP daytime, VLF 24-h, VLF daytime. Reduction of these frequency HRV characteristics may indicate autonomic neuropathy in patients with poor control of T1DM.*

Реферат. Зависимость вариабельности сердечного ритма от показателей контроля сахарного диабета 1 типа. Перцева Н.О., Гуржий Е.В., Мошенец Е.И. *Цель исследования – оценить влияние основных показателей контроля и течения сахарного диабета (СД) 1 типа на вариабельность сердечного ритма (ВСР). Обследовано 62 пациента с СД 1 типа в возрасте 18-45 лет со средней длительностью заболевания 11,0 (5,0; 18,0) лет. Оценка ВСР во временном и частотном диапазонах производилась путем анализа 24-часовой записи электрокардиограммы (ЭКГ) по Холтеру. В качестве маркеров, характеризующих течение и компенсацию СД 1 типа, использовались следующие лабораторные показатели: С-пептид, HbA1c, креатинин крови, альбуминурия (АУ), скорость клубочковой фильтрации (СКФ) рассчитывалась по формуле CKD-EPI. Кроме того, учитывались максимальное и минимальное значение гликемии, а также размах гликемии (разница между максимальным и минимальным значением гликемии), регистрируемые параллельно с 24-часовой записью ЭКГ с помощью системы длительного мониторинга гликемии iPro2 (Medtronic MiniMed, USA). Всем пациентам проводилась эхокардиография для исключения органической патологии сердца и ее возможного влияния на показатели ВСР. У пациентов с СД 1 типа недостаточный гликемический контроль оказывает негативное влияние на ВСР в виде снижения как частотных, так и временных характеристик ВСР. Размах гликемии может являться дополнительным негативным фактором влияния на сердечную деятельность у больных СД 1*

типа, независимо от уровня HbA1c, поскольку положительно коррелирует с показателями LF/HF сутки, ρ=0,43 (p<0,05), LF/HF день ρ=0,37 (p<0,05), ρ=0,38 LF/HF ночь, отражающими относительную гиперсимпатикотонию. Диабетическая нефропатия является еще одним фактором прогрессирования сердечно-сосудистых заболеваний при СД 1 типа, ввиду того, что ее критерии достоверно коррелируют обратными (для СКФ) и прямыми (для АУ) связями средней силы со всеми характеристиками ВСР. Анализируемые показатели контроля СД 1 типа обусловливают ВСР на 45,73%, в наибольшей степени влияя на TP сутки, TP день, VLF сутки, VLF день. Снижение данных частотных характеристик ВСР может свидетельствовать о формировании кардиальной автономной нейропатии у пациентов с недостаточным контролем СД 1 типа.

The importance of heart rate variability (HRV) is in the changeability in the duration of consecutive cardio-intervals, it reflects the functional ability of the cardiovascular system to adapt to external and internal environmental factors. This variability is normally caused by the balanced influence of the sympathetic and parasympathetic nervous systems [9, 15]. Interest in HRV has a long history and, thanks to numerous studies, especially in the last 30 years, the prognostic significance of its reduction in patients with myocardial infarction, congestive heart failure, ventricular arrhythmias and sudden cardiac death has been proven [6,10, 12]. A meta-analysis of 8 HRV studies in a cohort without cardiovascular pathology conducted by Hillebrand S. and colleagues found that a lower HRV was associated with an increase in the risk of the first cardiovascular event by 32-45% and an increase in HRV due to the SDNN index by 1% reduces the occurrence of fatal and non-fatal cardiovascular diseases (CVD) by about 1% [10].

Particular attention is paid to the analysis of HRV in diabetes mellitus (DM), where damage to the autonomic heart is associated mainly with the development of diabetic neuropathy (DN). Type 1 diabetes is associated with a 2-4-fold increase in mortality risk, with fatal and non-fatal cardiovascular events occurring in these patients on average 10-15 years earlier than in the general population. The prevalence of cardiovascular autonomic neuropathy (CAN) varies greatly because of differences in criteria when diagnosing and ranges from 2.5% to 90% in patients with type 1 diabetes and from 25% to 75% in patients with type 2 diabetes [10, 13]. According to the results of a meta-analysis of 15 studies, the relative risk of mortality of patients with DM by cardiovascular tests established by the impairment of the autonomic support of cardiovascular activity is 3.65 compared with patients without signs of CAN [8].

The development of CAN is certainly facilitated by the long course of the disease and the lack of compensation for carbohydrate metabolism, which was confirmed in the EURODIAB study. According to its results, CAN correlated with the severity of diabetic microvascular complications (retinopathy and nephropathy) [4]. The importance of achieving target glycemia to prevent the formation and progression of CAN was demonstrated in the DCCT/EDIC study [5].

Therefore, a comprehensive study of the effects of type 1 diabetes on the functional state of the cardiovascular system will help to determine the main factors for the formation and progression of CVD, and in the future - to develop means of their prevention in these patients, which can improve the quality and life expectancy. The purpose of our study was to evaluate the effect of major indicators of control and course of type 1 diabetes on heart rate variability.

MATERIALS AND METHODS OF RESEARCH

The study was conducted on the basis of the endocrinological unit of the clinic of Medical Academy (Dnipro) during 2016-2017, in compliance with the ethical norms and principles of Helsinki Declaration of the World Health Association on conducting scientific medical research with human participation. Before the examination all patients signed a voluntary informed consent, approved by the bioethics committee of Dnipropetrovsk Medical Academy of Health Ministry of Ukraine..

Diagnosis of type 1 diabetes was established according to the diagnostic criteria of the American Diabetes Association (ADA) of 2016 and the unified clinical protocol of primary, emergency, secondary (specialized) and tertiary (highly specialized) medical care “Diabetes mellitus type 1 in young people and adults” № 1021 from 29.12.2014 [3, 14].

A total of 62 patients with diabetes mellitus aged 18 to 45 were examined, of whom 37 (59.68%) were women and 25 (40.32%) – men. Disease duration is 11.0 (5.0; 18.0) years, body mass index (BMI) – 23.06 (20.81; 24.08) kg/m^2. All patients underwent insulin therapy according to the baseline-bolus regimen, daily insulin dose is 45 (35.0; 58.0) IU.

Exclusion criteria: type 2 diabetes; diabetic ketoacidosis at the time of inclusion; secondary diabetes; BMI> 40; diabetic proliferative retinopathy; diabetic nephropathy IV and V; diabetic foot (class II and higher by Wagner); heart failure III, IV by NYHA; hypertension, resistant form; congenital and ac-

quired heart defects; acute coronary syndrome, acute cerebral circulation disorder and transient ischemic attack; the period of exacerbation of concomitant chronic pathology; acute somatic diseases; history of myocarditis; glomerular filtration rate (GFR) <45 ml/min; oncological diseases up to 5 years from the full course of therapy; antiretroviral therapy; diagnosed viral hepatitis B and C; pregnancy.

Laboratory data analysis included determination of HbA1c, C-peptide, blood creatinine, albuminuria (AU) and long-term glycemic monitoring. HbA1c concentration, blood creatinine and AU level were determined by photocolorimetric method using an automatic biochemical analyzer SAPPHIRE 400, Tokio Boeki, Japan, 2009. GFR was calculated using the CKD-EPI formula. C-peptide was determined on a COBAS e411 immunochemical electrochemiluminescent automatic analyzer, Roche Diagnostics GmbH & amp; Hitachi, Japan, 2012. Long-term glycemic monitoring was performed using an iPro2 system (Medtronic MiniMed, USA). The maximum and minimum glycemic value, as well as the range of glycemia (the difference between the maximum and minimum glycemic value) were taken into account.

In parallel with the long-term blood glucose monitoring, a daily electrocardiogram (ECG) monitoring was performed by Holter in three modified leads: MV4, Y, MV6 for 24 hours on the SDM23 apparatus (manufacturer: LLC "IKS-Techno" Ukraine) in terms of free movement mode. The time and spectral parameters of the HRV were studied, which were calculated using the ARNIKA software version 8.3.9.

Time domain analysis was performed using SDNN, RMSSD, PNN50% indicators. The HRV spectral analysis included an estimation of the power of the four main frequency bands in ms^2: high frequency (HF) – 0.15-0.40 Hz, low frequency (LF) spectrum of very low frequency (VLF), as well as the total power of the spectrum and the ratio of low frequency components to high frequency components (LF/HF).

To exclude organic cardiac pathology that could affect HRV indices, echocardiography was performed using a standard Philips HD3 apparatus using a C4-2 sensor.

Statistical processing of the results was performed using Microsoft Excel (Office Home Business 2KB4Y-6H9DB-BM47K-749PV-PG3KT) with the AtteStat software add-on and STATISTICA 6.1 software (StatSoftInc., Serial No. AGAR909E415822FA). Median (Me) and interquartile range (25%; 75%) were used to describe the sample abnormal distribution of quantitative variables; to analyze the relationships between different variables – correlation analysis with the calculation of Spearman rank correlation coefficients (ρ). Correlation coefficient in the range of $0.7 \leq |\rho| < 1$ indicated a strong correlation; $0.3 \leq |\rho| < 0.7$ – moderate; $0 < |\rho| < 0.3$ – weak correlation [1].

RESULTS AND DISCUSSION

Among the surveyed patients, 18 (29.03%) patients (HbA1c≤7.0%) were compensated and 44 (70.97%) had decompensation of type 1 diabetes. Hypoglycaemic states which were determined in case of decrease in glycemia less than 3.9 mmol/l were reported in 27 (43.55%) patients. 29 (46.77%) patients had moderate AU and 3 more (4.84%) – expressed AU. According to HRV spectral analysis, patients had a predominance of sympathetic effects on cardiac activity.

General characteristics of laboratory findings and diurnal values of HRV are shown in Table 1.

Relationship between T1DM control and course and values o HRV were assessed first in priority using rank correlation (Table 2).

The data obtained determine the presence of numerous significant negative correlations mainly of the mean force between carbohydrate metabolism (HbA1c level and glycemia range) and virtually all, both time and frequency, HRV characteristics.

As can be seen from Table 2, the GFR and AU indicators on which the diagnosis of diabetic nephropathy (DN) is based also correlated significantly with all the studied characteristics of HRV. DN is one of the manifestations of microangiopathy, which in type 1 diabetes has a generalized character and underlies the pathogenesis of all chronic diabetic complications [2, 11]. Accordingly, since the severity of DN reflects the state of the microcirculatory bed as a whole, the results obtained by us coincide with the literature data regarding the mechanism of myocardial lesions due to hyperglycemia [2, 7, 16].

For the complex evaluation of the obtained data, the transformation of the primary data by the Box-Cox method was used to obtain the normal distribution of variables and the canonical correlation analysis was performed for the HRV variables: diurnal SDNN, SDNN day, SDNN night, diurnal RMSSD, RMSSD day, RMSSD night, diurnal pNN50%, pNN50% day, pNN50% night, diurnal TP, TP day, TP night, diurnal VLF, VLF day, VLF night, diurnal LF, LF day, LF night, diurnal HF, HF day, HF night, diurnal LF/HF, LF/HF day, LF/HF night and laboratory findings: minimum and maximum glycemia, glycemia, HbA1c, C-peptide, creatinine, GFR and AU.

Table 1

Characteristics of laboratory findings of T1DM control and course and diurnal values of HRV (median and interquartile range Me (25%;75%))

Findings of T1DM control	
HbA1c, %	9.8 (7.4; 11.2)
C-peptide, ng/ml	0.01 (0.01; 0.15)
Blood creatinine, mcmol/L	94.6 (86.12; 103.35)
GFR(CKD-EPI), ml/min/1,73m^2	76 (67; 85)
Albuninuria, mg/L	30.3 (16.8; 44.7)
Glycemia min., mmol/L	4.3 (2.75; 5.15)
Clycemia max., mmol/L	15.75 (12.3; 18.95)
Glycemia range, mmol/L	10 (7.4; 13.2)
Diurnal values of HRV	
SDNN diurnal, mc	122 (104; 156)
RMSSD mc, diurnal	28 (22; 43)
pNN50 diurnal, %	5 (3; 13)
TP diurnal, mc^2	6754 (3959; 10720)
VLF diurnal, mc^2	4288 (2555; 6576)
LF diurnal, mc^2	1886 (976; 3472)
HF diurnal, mc^2	504 (216; 1051
LF/HF diurnal	4,1 (2.7; 5)

As a result of the canonical correlation analysis, seven canonical roots were calculated, of which only one was statistically significant (p=0.001). The canonical correlation coefficient between HRV and laboratory findings is R=0.82 (χ2=261.76; p=0.001). This suggests that there is a strong relationship between the weighted sums of laboratory findings (minimum and maximum glucose levels, glycemia, HbA1c, C-peptide, creatinine, GFR and AU) and weighted amounts of HRV.

Table 2

Correlations between laboratory findings and results of heart rate variability by ECG (Spearman's rank correlation coefficient – ρ)

Findings	Glycemia range	HbA1c	creatinine	GFR	AU
SDNN diurnal, mc	-0.24*	-0.26*	-0.16	0.26*	-0.35*
SDNN day, mc	-0.2	-0.22	-0.22	0.34*	-0.25*
SDNN night, mc	-0.38*	-0.27*	-0.17	0.31*	-0.46*
RMSSD mc, diurnal	-0.33*	-0.22	-0.17	0.34*	-0.45*
RMSSD day, mc	-0.23	-0.17*	-0.15	0.34*	-0.37*
RMSSD night, mc	-0.29*	-0.28*	-0.21	0.35*	-0.38*
pNN50 diurnal, %	-0.3*	-0.22	-0.14	0.34*	-0.37*
pNN50 day, %	-0.22	-0.19	-0.13	0.35*	-0.3*
pNN50 night, %	-0.3*	-0.23	-0.17	0.33*	-0.38*
TP diurnal, mc^2	-0.24	-0.29*	-0.21	0.38*	-0.33*
TP day, mc^2	-0.19	-0.34*	-0.26*	0.43*	-0.28*
TP night, mc^2	-0.19	-0.2	-0.15	0.27*	-0.32*
VLF diurnal, mc^2	-0.15	-0.26*	-0.14	0.32*	-0.25*
VLF day, mc^2	-0.13	-0.3*	-0.21	0.36*	-0.2
VLF night, mc^2	-0.26*	-0.31*	-0.21	0.34*	-0.38*
LF diurnal, mc^2	-0.33*	-0.34*	-0.24	0.46*	-0.41*
LF day, mc^2	-0.22	-0.3*	-0.24	0.42*	-0.32*
LF night, mc^2	-0.3*	-0.28*	-0.24	0.34*	-0.38*
HF diurnal, mc^2	-0.4*	-0.28*	-0.3*	0.39*	-0.44*
HF day, mc^2	-0.35*	-0.31*	-0.31*	0.4*	-0.38*
HF night, mc^2	-0.39*	-0.26*	-0.3*	0.38*	-0.43*
LF/HF diurnal	0.43*	0.16	0.32*	-0.26*	0.36*
LF/HF day	0.37*	0.2	0.28*	-0.2	0.29*
LF/HF night	0.38*	0.16	0.35*	-0.3*	0.31*

Note. * – correlation coefficient at a level of statistical significance $p<0.05$.

The obtained canonical roots extract 100% of dispersion from the left set of variables (laboratory findings) and 45.03% from the right set of variables (HRV values), that is, eight independent canonical variables (minimum and maximum glucose levels, glycemia, H1 glycemia, creatinine, GFR, and AU), capable of explaining 100% of changeability of referred laboratory findings, and the analyzed HRV values can explain 45.03% of the variability of this group of findings.

The factor structure and the canonical weights for the variables are shown in Table 3.

Table 3

Factor structure and the canonical weights for the variables characterizing laboratory findings and HRV values in the study subjects

Findings	Canonical weights	Structure coefficients	Explained variance	Total redundance
Left set of findings (laboratory findings)				
Minimal glycemia	-1.526	-0.028	100.0 %	45.73 %
Maximal glycemia	2.821	-0.662		
Glycemia range	-2.731	-0.650		
HbA1c	-0.021	-0.612		
C-peptide	1.015	0.991		
Creatinine	-0.147	-0.478		
GFR	-0.049	0.524		
AU	0.083	-0.180		
Right set of findings (HRV values)				
SDNN diurnal	0.235	0.506	45.03 %	29.41 %
SDNN day	-0.22	0.421		
SDNN night	0.268	0.599		
RMSSD diurnal	-0.399	0.667		
RMSSD day	-0.029	0.541		
RMSSD night	-0.175	0.627		
pNN50% diurnal	-0.256	0.451		
pNN50% day	-0.015	0.434		
pNN50% night	-0.09	0.441		
TP diurnal	5.643	0.422		
TP day	-14.363	0.356		
TP night	-1.682	0.460		
VLF diurnal	-9.485	0.303		
VLF day	18.225	0.320		
VLF night	-1.288	0.533		
LF diurnal	1.842	0.640		
LF day	-0.764	0.484		
LF night	0.049	0.521		
HF diurnal	1.18	0.720		
HF day	2.309	0.605		
HF night	-0.838	0.589		
LF/HF diurnal	-0.307	-0.377		
LF/HF day	0.219	-0.360		
LF/HF night	0.096	-0.263		

Of the laboratory findings, C-peptide (structural coefficient 0.991), maximum glucose level (-0.662), glycemia range (-0.659), HbA1c (-0.612), GFR (0.524) have the highest load on the first canonical factor. These indicators strongly and moderately correlate with the combined factor - laboratory findings.

Among HRV values, HF day, RMSSD day, LF day, RMSSD night, HF day, SDNN night and HF night the most strongly correlated with the first canonical root (indicated factor), load of canonical factors being 0.720; 0.667; 0.640; 0.627; 0.605; 0.599; 0.589 respectively.

The greater the absolute value of the canonical weight, the greater the contribution of the corresponding indicator to the value of the canonical variable, so the greatest contribution to the group of left-set indicators (laboratory values) is the maximum glucose level and glycemic range. In the right set of indicators (HRV values), the largest contribution to the value of the canonical variable is made by TP day and night, TP day, VLF day and night, VLF day.

As a result of our study, about 45.73% of dispersion of HRV values can be explained by the values of the variables from the left set of indicators (laboratory findings), 29.41% of the variance of laboratory findings can be explained by the values of the right indicators (indicators of HRV).

CONCLUSIONS

1. In patients with T1DM, insufficient glycemic control has a negative effect on HRV, reducing both frequency and time characteristics of HRV.

2. Glycemia range correlates positively with LF/F day, $\rho=0.43$ ($p<0.05$), LF/HF day $\rho=0.37$ ($p<0.05$), $\rho=0.38$ LF/HF night, the growth of which reflects relative hypersympathicotonia. Therefore, this finding may be an additional negative factor affecting cardiac activity in patients with T1DM, regardless of the level of HbA1c.

3. Diabetic nephropathy can also be considered a factor in the progression of CVD in T1DM, as its criteria correlate significantly with inverse (for GFR) and direct (for AU) relationships of average strength with all HRV characteristics.

4. The canonical correlation analysis found that findings of T1DM control predetermine HRV by 45.73%, most influencing diurnal TP, TP day, diurnal VLF, VLF day. A strong statistically significant relationship was found between HRV and DM 1 control rates (HbA1c, C-peptide, blood creatinine, GFR, MAU, minimal glycemia, maximum glycemia, and glycemia).

5. The results obtained as for reducing TP and VLF may indicate the formation of cardiac autonomic neuropathy in patients with insufficient control of T1DM.

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