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Diabetes & its Complications

Indicators of Autonomic Regulation in Evaluating Prognostic Risk in Patients with Diabetes

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ABSTRACT

Background: *The study of the state of the autonomic nervous system in diabetic patients is not an easy task. The nervous system suffers quite often in this disease, especially when the diabetes is unsatisfactory. However, the nervous system retains the regulatory function. What effect does cardiac autonomic neuropathy have on the course of the disease and the prognosis - is a problem that requires a thorough and thorough study.*

Methods: *Across sectional study was conducted in the endocrinology department of the clinical hospital. 247 patients were examined. The vegetative status of patients with different types of diabetes, the different duration of the disease and the level of comorbidity were studied.*

Results: *Atered heart rate variability associated with the development of diabetic patient's autonomic neuropathy qualitatively affects the prognosis of the disease, reducing the patient's functional reserves. The efficacy of treatment of diabetic neuropathy in these patients was determined by the degree of preservation of the biological component rehabilitation potential (morpho-functional index). The study of the effectiveness of ACE inhibitors in patients with diabetic cardiac autonomic neuropathy (CAN), depending on the state of metabolic compensation, vegetative balance and adaptive capabilities of the patient with diabetes.*

Conclusions: *A high voltage of humoral metabolic processes provided the obtained data showed that the presence of cardiac autonomic neuropathy, even against the background of diabetes compensation, led to high activity of central energy-consuming mechanisms of regulation and vegetative dysfunction, and the state of sub compensation.*

Keywords
Diabetes mellitus, Autonomic dysfunction, Cardiac autonomic neuropathy, Functional body reserves, Autonomic regulation.

Background
Already in the debut of the disease, diagnosed neuropathy set 27% of patients with DM1 and 35 % of patients with DM2 [1-3]. The autonomic nervous system is the most important regulating mechanism of the organism's activity. By the speed of response to changes in external and internal conditions, it significantly exceeds the metabolic and hormonal regulation. The degree of tension of regulatory systems is determined by the tone of the autonomic nervous system and affects the level of functioning of the blood circulation. Particular importance vegetative status has in diabetes mellitus, as if, Hyperglycemia also depends, and determines the activity of the sympathetic system at the same time. Good compensation of diabetes mellitus (DM) improves the course of neuropathy and helps to reduce the frequency of these complications. The tone of the vegetative system is labile and can be used both to control the course of diabetes, and to control the effectiveness of ongoing therapeutic and rehabilitation activities.

Purpose of study
To determine the prediction of autonomic regulation parameters in diabetic patients and to identify the most important forecast parameters of vegetative regulation in patients with diabetes

mellitus (DM).

Methods

Design

Patients hospitalized in a specialized endocrinology department of the hospital with a diagnosis of diabetes mellitus were subjected to a single-stage epidemiological study (cross-sectional observational study) with an emphasis on the state of indices of vegetative regulation. Individual groups of patients underwent dynamic observation. The study was conducted from 2010 to 2015.

Sampling and Setting

The study was conducted based on the Endocrinology Department of City Clinical Hospital name Eramishantsev (Moscow) and endocrinology department of the Regional Clinical Hospital (Izhevsk). A total number of 247 faculty members were recruited by using simple random sampling. The inclusion criteria – Patients of both sexes with metabolic syndrome and type 1 and type 2 diabetes aged from 20 to 65 years. Exclusion criteria – Age younger than 20 years, patients admitted in a state of ketosis or ketoacidosis. The basis for including patients in the study was also the informed consent of the patient.

Ethical Consideration

The study was conducted in compliance with the principles of medical ethics. The compliance of the study with the norms of biomedical ethics is confirmed by the conclusion of the Ethics Committee of the Medical Institute of the Peoples' Friendship University of Russia (Protocol №9, of Marth 17, 2016) and the Izhevsk Medical Academy (Protocol №123, February 18, 2009). Participants were fully acquainted with the objectives of the study, its importance, the method of selecting participants, the right to refuse to participate at any time, the benefits and risks of the study.

Instruments and Data Collection Procedure

Glucose level was controlled according to WHO recommendations: Glucose profile; Glycated Hemoglobin (HbA1c). Criteria of compensatory DM type 2 are determined according to European Association for the Study of diabetes [2015]. To evaluate heart rate variability in spectral analysis (Valenta). Indicators of spectral analysis: GP, HF, LF, VLF, ULF (mc²) or HF (%), LF (%), VLF (%), ULF (%). The analysis was carried out with the calculation of the power spectrum of slow oscillations in four frequency ranges: very low frequencies - VLF; low frequencies - LF; high frequencies – HF. The allocation of the four frequency ranges is due to the difference in their formation: the very low frequency range reflects the functional state of the super segmentary structures. Range of low frequencies - the activity of the sympathetic system (increased normal, lower stress, diseases of the cardiovascular system) and the range of high frequencies - the activity of the parasympathetic nervous system at the segmental level. HF – reflects the activity of parasympathetic cardioinhibitory center of the medulla oblongata. Improvement at rest, reduction in stress, diseases of the cardiovascular system. The estimation of the indicators was carried out taking into account absolute and the relative power values of the spectrum of each frequency range (VLF, LF, HF). GP reflects the total effect of exposure on heart rate at all levels of regulation. Reduced at low stress resistance of the organism. Index of vegetative balanced (IVB) - LF/HF is a power ratio of waves of low frequency (LF) power to high-frequency waves (HF). Increase – Predominance of sympathetic activity. Decrease – when activated parasympathetic system. IC (index of centralization) = (LF+VLF)/HF – shows the ratio of the activity of the Central contour of regulation to Autonomous. It is calculated by dividing the sum of the capacities of low-frequency waves (LF and VLF) to the power of the waves of high frequency (HF).

To assess the prognosis of the disease- morphological function index – MFI as component of the rehabilitation potential (patent № 2344751RU, 2009y. “The method of determining the biological component of the rehabilitation potential of patients with diabetes” and patent № 2007613898 “Software determine the level of morpho-functional index of the patient and rehabilitation prognosis”)

$$\frac{0{,}011P - 0{,}0101P^{*} + 0{,}014S - 0{,}0129S^{*} + 0{,}008D - 0{,}0074D^{*} + 0{,}0011A + 0{,}009W - 0{,}0083W^{*} - 0{,}0007H - 0{,}302}{0{,}7343 - 0{,}00178P^{*} - 0{,}00226S^{*} - 0{,}00129D^{*} - 0{,}00226A - 0{,}00145W^{*} + 0{,}00145H}$$

P-The heart rate is the actual average for the day (beats / min.);
*P * - the pulse rate is ideal within the limits of the age norm (beats / min.)*
SBP - the systolic blood pressure actual on the average for a day (mm of mercury);
*S * - systolic blood pressure is ideal by age (mm Hg)*
DBP - the diastolic blood pressure actual on the average for a day (mm of mercury);
*D * - diastolic blood pressure is ideal*
W - actual body weight at the time of examination (kg);
*W * - ideal body weight (kg), which is determined by the formula*
A - the actual age (the number of full years at the time of the survey in years);
H - growth of the patient at the time of the examination (cm).

According to formula, which are already used, those are Heart Rate, Systolic & diastolic blood pressure, AGE, body mass, height. All parameters, which are given in slide/ actual parameters are compared with parameters of the same patient, if he would have been in healthy (ideal) condition (deviation from the norm). MFI - an inverse value to rehabilitation potential. The more the deviation (size MFI), is lower rehabilitation potential. The method of computer modeling allowed transforming the obtained results into a form convenient for interpretation (0-1).

Range of MFI

- MFI ≤ 0 - good compensation of diabetes, favorable course, biological component of RP high, rehabilitation prognosis favorable;
- 0 ≤ MFI <1 - satisfactory compensation of diabetes, biological component of RP satisfactory, rehabilitation prognosis relatively favorable;
- MFI ≥ 1 - unsatisfactory compensation of diabetes, multiple complications, biological component of RP low, unfavorable prognosis;

The computer program developed made the formula easy to use. We took out the patent for this method of assessment of rehabilitation opportunities of an organism.

Data Analysis Procedures

Processing of received data - Program STATISTIC 10,0 (Matematica®, Matlab®, Harvard Graphics®) StatSoft). Descriptive statistical measures including frequency and percentages were used to describe. Moreover, mean, median, range, and percentages statistics were used to calculate vegetative measurements. The Chi square test inferential statistic was used for testing associations between some measurements. A P-value of < 0,05 was considered to be significant.

Results

Heart rate variability and quality of diabetes mellitus

Daily monitoring of the ECG showed that unsatisfactory compensation of diabetes mellitus led to significant changes in the parameters of heart rate variability (HRV), But the direction and severity of the disorders in patients with different types of diabetes was not the same (Figure 1). Like, Circadian index (CI) in patients with type 2 diabetes was very low - 1,19 ± 0,08, which is possible only with a marked violation of the central and vegetative regulating the heart rate. The power of the low-frequency spectrum (LF-24.2 ± 2.1%, VLF-23.4 ± 3.7%, ULF-30.8 ± 8.4%) prevailed over the high-frequency power (HF-21.6 ± 2.9%), which is typical for pronounced vegetopathy and failure of vegetative regulation. In this case, the age of the patient and the duration of diabetes had no fundamental importance. Unsatisfactory compensation of type 1 diabetes did not affect CI (1.3 ± 0.17), but was accompanied by a decrease in the total spectrum power (TC 1675 ± 233 ms^2). The predominance of the power of the low-frequency spectrum (ULF-36.5 ± 11.0%, VLF-33.9 ± 4.7%, LF-17.4 ± 6.9%) over the high-frequency spectrum (HF-11.7 ± 1.5%). The coefficient of the vegetative sympathetic balance of patients with type 1 diabetes on the background of unsatisfactory compensation (LF/HF) was above the average of 1.58 ± 0.4, confirming hyper sympathetic tone (Figure 2). In patients with type 2 diabetes, the unsatisfactory quality of diabetes compensation was also accompanied by a vegetative imbalance, but against a background of increased activity of the parasympathetic nervous system (LF/HF-0.92 ± 0.07). In the course of treatment in patients with type 1 diabetes, the TS increased to 6157 ± 311 ms2, which indicated an increase in the adaptive capacity of the organism and restoration of the vegetative balance. The level of HF-18.4 ± 1.9% increased and the LF/HF-value was 1.23 ± 0.14. The power of VLF decreased somewhat (25.6 ± 4,4%), LF and ULF values did not change reliably. In patients with diabetes 2, active rehabilitation measures contributed to an increase in CI to 1.29 ± 1.1 (in the comparison group, 1.22 ± 0.7). The values decreased like HF from 21,6 ± 3,3% to 11,8 ± 1,9%, and LF from 24.2 ± 12.1% to 12.6 ± 4.7%, which led to a decrease in parasympathetic activity And normalization of the vegetative balance (LF/HF-1.32 ± 0.3), but, simultaneously, it also indicated the progression of organic disorders in the cardiovascular system. MFI within the limits of normal values was observed only in patients with DT1 satisfactory compensation. MFI is a dynamic indicator for patients with a sufficient level of preservation of the rehabilitation capabilities of the body. It can be used not only for diagnosis, but also for monitoring therapy (Figures 2 and 3).

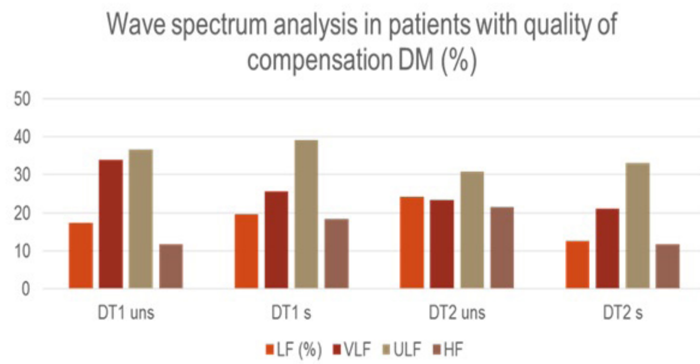

Figure 1: Wave spectrum analysis in patients depending on the quality of diabetes compensation. Uns - Patients with unsatisfactory compensation of diabetes (HbA1c≥7,5%); S - patients with satisfactory compensation of diabetes (HbA1c<7,5%).

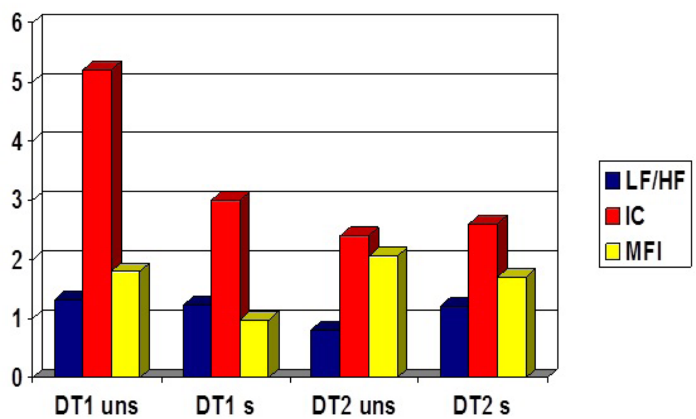

Figure 2: The variability ratios and MFI in patients with different type and severity of DM. Uns - Patients with unsatisfactory compensation of diabetes (HbA1c≥7,5%); S - patients with satisfactory compensation of diabetes (HbA1c<7,5%).

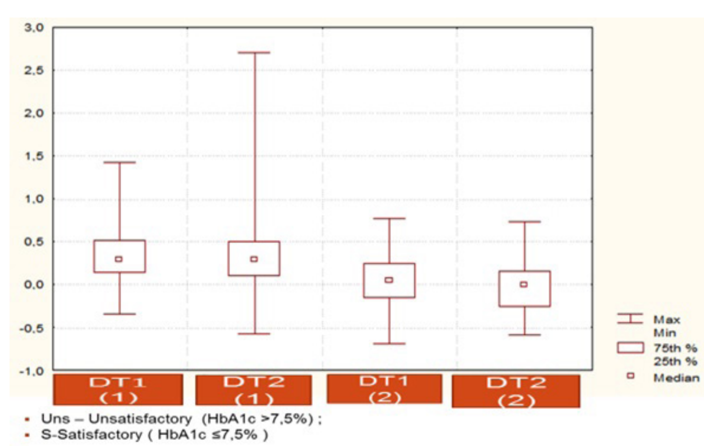

Figure 3: The MFI dynamics in the course of treatment. Uns - Patients with unsatisfactory compensation of diabetes (HbA1c≥7,5%); S - patients with satisfactory compensation of diabetes (HbA1c<7,5%).

Variability of the heart rate and functional reserves of the body

The indicator made it possible to characterize the features of the course of diabetes mellitus. The obtained results confirmed the connection between the severity of diabetes mellitus and the adequacy of metabolic control, which is especially significant in patients with moderate type 2 diabetes and severe. With an easy course of DM type 2, patients usually had a duration of DM of less than 3 years, and the group itself was small for high-precision statistical analysis. Separately, a group of patients with type 1 of moderate severity should be considered. Of 87 patients in the observation group, 37 patients (42.5%) had a duration of diabetes less than 5 years without diagnosed vascular complications and, despite poor compensation, the MFI index was <0 in 23 people (26.4%). It was these patients that significantly changed the reliability of the difference between the groups. In 33 patients (38%) 0≥MFI ≤ 1, in 31 patients (35.6%) the MFI was more than one. The rehabilitation potential turned out to be directly correlated with the compensation of diabetes mellitus, the presence of arterial hypertension and the morphophysiological index. It was found that unsatisfactory compensation of diabetes mellitus led to significant changes in heart rate variability, but the direction and severity of disorders in patients with different types of diabetes was not the same (Figure 4). The obtained results allow considering that the circadian index, GP, LF/HF, HF%, LF%, VLF%, ULF% and integral indices have the greatest value in assessing the vegetative status. It is advisable to use different indicators as criteria for assessing vegetative status in patients with different types of diabetes. The prognostic risks of an unfavorable rehabilitation prognosis according to the indices of rhythm variability were studied (MFI≥1) patients with DT1- TC <1500 ms² (RR = 2.5), VLF <50% in the structure of the spectrum (RR=1.46), LF/HF ≥3.0 (RR=1.77), IC ≥3.50 (RR=3.52), the index of regulatory systems tension (RR=3.1). In patients with DT2, symptoms of autonomic dysfunction are observed with the onset of the disease.

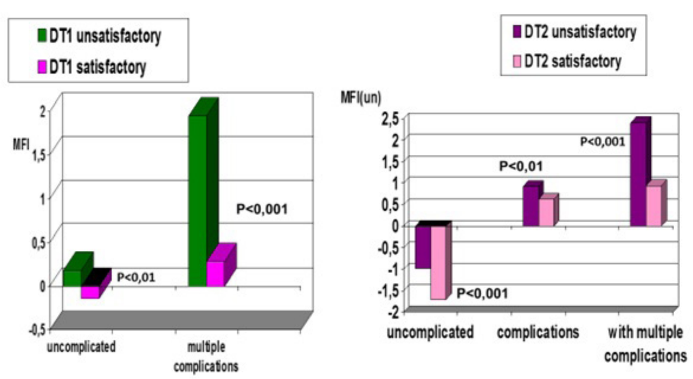

Figure 4: MFI in patients with different type and severity of DM.

Variability of heart rate, safety of functional reserves and efficiency of treatment of diabetes mellitus and its complications

Comparative analysis of spectral characteristics was carried out in patients with type 2 diabetes with comorbidity diseases - 28 patients with a diagnosis of HTN of 2 items, risk of IV and 17 patients with chronic diseases of the digestive system. LF/HF, HF%, LF%, VLF%, ULF%, and the IC centralization index (LF+VLF/HF) were estimated. In the DT2 + HTN surveillance group, the directionality of regulatory processes also indicated chronic stress (LF ↑ HF ↓), while VLF% and ULF% were increased (reflects the activity of higher centers of control of heart rhythm), but did not reach the level of confidence in the comparison group. We can only talk about the tendency to centralize the mechanisms of regulation. However, these data confirm the primary of HTN in the pathogenesis of deregulation in the group of DM + HTN (Figure 5).

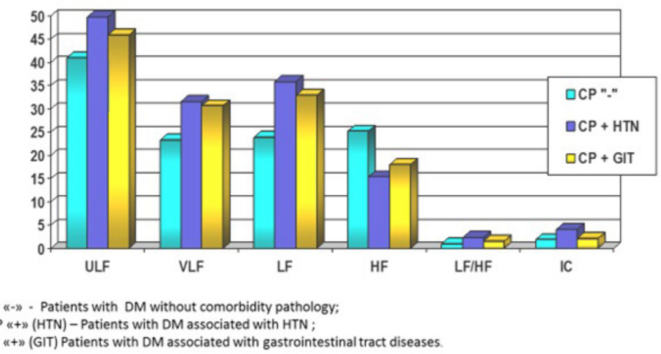

Figure 5: Spector of frequency range in comorbidity of type 2 diabetes.

ULF - the power of the wave's ultra-low frequency reflects the activity of higher centers of control of heart rhythm. Improvement: typical of disruption of autonomic regulation.

In the group of patients with diabetes, the increase in LF (38.5 ± 12.7%) was observed, which is characteristic of chronic stress, which is significantly higher than in the comparison group (p=0.001; r=0.31). Decrease in HF (15.4 ± 5.5%) is a predictable process, often observed in patients with cardiovascular pathology and also indicates a state of chronic stress. The level of ULF%, which in patients with diabetes in the comparison group was already above the normal values, was even higher in patients with arterial hypertension (p=0.0002; r=0.48), which is characteristic for the failure of vegetative regulation. In two patients from this group, the values of ULF (%) occupied almost the entire spectrum (76% and 91%). In both cases, patients died of acute vascular "catastrophes" during a half-year of inactive for active therapy with antihypertensive drugs. In the group of patients with arterial hypertension, activation of central ergotropic and humoral metabolic processes (VLF 31.5 ± 7.3%) was observed, exceeding the value not only in the comparison group (p=0.001; r=0.37), but also standard indices Healthy individuals (28.6 ± 11.2%). This indicator demonstrates the practically direct effect of arterial hypertension on metabolic homeostasis in patients with diabetes and explains the reasons why it is difficult to achieve satisfactory compensation of diabetes in patients with coexisting AH. And also explains one of the mechanisms of progression of complications of diabetes in patients with arterial hypertension. The elevated level of IC (4.1 ± 0.9) in the DT2 + HTN group confirmed the high activity of the central regulation loop in relation to the autonomic.

In the DT2 + PPP surveillance group, the directionality of regulatory processes also indicated chronic stress (LF ↑ HF ↓), while VLF% and ULF% were increased, but did not reach the level of confidence in the comparison group. We can only talk about the tendency to centralize the mechanisms of regulation. However, these data confirm the primacy of AH in the pathogenesis of deregulation in the group of DM + HTN.

In assessing the effectiveness of antihypertensive therapy, a significant factor is the level of rehabilitation potential. Regardless of the type of disease, normodipity was achieved in groups of patients with a high level of rehabilitation capabilities. Of the number of patients with low rehabilitation potential, normodipity in patients with metabolic syndrome was 28.5%. In 44% of patients with type 2 diabetes, normal BP values were not obtained as a result of the treatment.

The negative influence of metabolic disturbances on body reserves was reflected in the decrease in the effectiveness of antihypertensive therapy. Almost half of patients with diabetes mellitus with a low level of rehabilitation potential required combined antihypertensive therapy, which included three or more drugs (Figure 6).

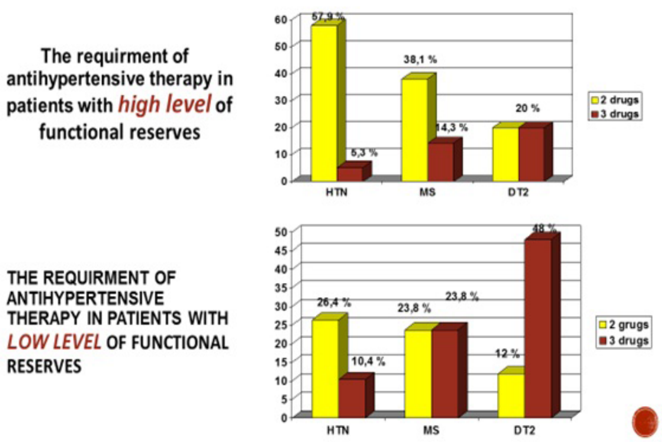

Figure 6: The requirement of antihypertensive Therapy.

We have already mentioned that drug therapy is also an external effect on which an organism with a modified regulation system may not always react as planned. ACE inhibitors are widely and successfully used in the treatment of diabetes mellitus, and we did not aim to study the efficacy of Ramipril on the progression of macrovascular complications of diabetes, believing this to be proven [HORE, 2000]. In this case, we set the task of studying the relationship between cardiac rhythm variability and rehabilitation capabilities of the body, patients with diabetes mellitus complicated by cardiac autonomic neuropathy (CAS), and the effectiveness of antihypertensive therapy with ramipril, depending on the degree of diabetes compensation (pic-7).

The state of autonomic regulation was studied in 19 patients with type 1 diabetes (mean age 37.0 ± 6.4) and 26 patients with type 2 diabetes (mean age 54.4 ± 5.9). As the main antihypertensive drug, all patients took ramipril at a dose of 1.25-2.5 mg once a day.

The design of the study involved not comparing the effectiveness of antihypertensive drugs with each other, but comparing the effectiveness of one drug in different conditions of the course of the disease. Was presented temporal and spectral analysis of heart rate variability (Tables 1 and 2).

Index	DM type1 (n=19)		DM type 2 (n=26)		Normal	
	Group A (n=11)	Group B (n=8)	Group A (n=14)	Group B (n=12)	30-39 years	50-59 years
CI	132,5±44,1*	128,1±21,8	119,3±28,6*	127,8±12,0	1,32±0,1	1,32±0,1
HR at noon	83,7±12,8*	88,1±19,1	82,6±7,4	84,1±4,9	78±7	76,9
HR at night	63,1±3,9	68,9±6,1	69,5±2,8	66,6±3,1		
SDNN all day	41,1±11,1*	20,4±9,0	65,0±8,7*	31,7±4,9	143±32	121±27
SDNN in a day	28,9±5,7	20,3±7,2	41,3±3,1*	31,0±3,8		
SDNN at night	16,1±6,7*	20,4±4,6	34,2±1,9	32,0±3,2		
SDANN all day	53,0±13,4*	42,6±4,9	77,4±15,1*	57,9±11,3	130±33	106±27
SDANN in day	63,7±10,0*	38,7±11,0	83,4±21,0*	55,0±12,7		
SDANN night	70,6±9,3*	45,7±10,2	72,9±18,0*	60,3±9,1		
pNN50% all day	8,2±1,1*	6,5±0,7	6,5±1,4	5,5±0,9	13±9	6±6
pNN50% day	4,9±1,3	4,4±0,2	6,2±0,9*	3,8±0,7		
pNN50% night	8,6±0,9	10,3±0,8	4,6±0,2	4,5±0,2		

Table 1: Temporal analysis of heart rate variability.
Group A – Patients with unsatisfactory compensation of diabetes (HbA1c≥7,5%); Group B - patients with satisfactory compensation of diabetes (HbA1c<7,5%); CI is the circadian index; HR - heart rate; * - p < 0,05.

Index	DM type 1 (n=19)		DM type 2 (n=26)	
CI	Group A (n=11)	Group B (n=8)	Group A (n=14)	Group B (n=12)
HR at day	132,5±44,1*	128,1±21,8	119,3±28,6*	127,8±12,0
HR at night	83,7±12,8*	88,1±19,1	82,6±7,4	84,1±4,9
HR minimum.	63,1±7,9	68,9±8,1	69,5±2,8	66,6±3,1
HR max.	54,2±1,7*	61,6±2,3	59,1±2,9	57,7±3,2

TP (мс²)	129,3±13,1*	137,4±9,9	131,8±7,1	128,6±13,0
ULF (%)	8741,6±112,7	7824,4±139,4	7433,4±212,3*	5274,5±149,8
ULF (мс²)	35,3±3,7*	42,6±2,5	32,1±2,9*	50,7±4,4
VLF (%)	1987,0±118,6*	2750,1±211,1	1684,5±143,5	2266,3±148,0
VLF (мс²)	39,3±4,9*	25,6±2,8	24,6±2,5	23,4±3,3
LF (%)	4394,5±312,1*	1940,5±159,0	2491,5±165,3*	1354,0±117,9
LF (мс²)	14,6±3,3*	17,5±5,1	25,3±4,7*	12,4±1,9
HF (%)	1456,0±137,3	1684,8±159,6	1542,7±201,0*	895,4±79,8
HF (мс²)	10,35±2,1*	14,2±1,8	21,0±3,7*	13,9±2,0
LF/HF	1104,1±58,8*	1604,2±117,1	1629,7±131,2*	759,3±48,9
IC	1,32±0,1	1,225±0,7	0,81±0,1*	1,21±0,05
MFI	5,2±0,8	3,0±0,07	2,4±0,2	2,6±0,7
	1,8±0,1*	0,97±0,2	2,05±0,05*	0,98±0,1

Table 2: Spectral analysis of heart rate variability.
Group A – Patients with unsatisfactory compensation of diabetes (HbA1c≥7,5%); Group B - patients with satisfactory compensation of diabetes (HbA1c<7,5%); CI is the circadian index; HR - heart rate; IC - index of centralization; MFI – morpho physiological index; * - p < 0,05.

The design of the study involved not comparing the effectiveness of antihypertensive drugs with each other, but comparing the effectiveness of one drug in different conditions of the course of the disease.

The power index of the very low frequency wave spectrum of VLF increased with poor compensation of diabetes, which reflected the involvement of central (over-segment) ergotropic and humoral-metabolic mechanisms in the regulation of the heart rhythm. Significant tension of adaptation mechanisms was confirmed by MFI>1. Against the backdrop of unsatisfactory compensation for type 1 diabetes, the power of the high-frequency and low-frequency spectrum decreased, the activity of the central contour of regulation increased (the increase in IC), the tone of the vegetative nervous system showed a predominance of sympathetic activity (increase in LF/HF). In patients with poor compensation of type 2 diabetes, the prevalence of parasympathetic activity (decrease in LF/HF) was noted when the power of the high (HF) and low frequency oscillation (LF). The values of the MFI indicator corresponded to the low level of rehabilitation opportunities for patients. The purpose of the ACE inhibitor affected not only the myocardial hemodynamic indexes, but also the state of vegetative balance and the rehabilitation potential of patients with diabetes with cardiac autonomic neuropathy (Table 3).

	DM type 1 (n=19)				DM type2 (n=26)			
	Group A (n=11)		Group B (n=8)		Group A (n=14)		Group B B (n=12)	
	1	2	1	2	1	2	1	2
TP (мс²)	8741,6±112,7*	7318,1± 213,4	7824,4± 139,4	7999,3± 176,0	7433,4± 212,3	7654,4± 131,1	5274,5± 149,8	5562,7± 317,0
VLF (%)	39,3±4,9*	21,4±5,5	25,6±2,8*	18,7±5,1	24,6±2,5	22,7±1,9	23,4±3,3*	17,4±2,9
LF (%)	14,6±3,3*	16,9±1,7	17,5±5,1*	24,4±4,7	25,3±4,7	21,9±4,3	12,4±1,9	16,3±4,5
HF (%)	10,35±2,1	13,7±3,4	14,2±1,8*	25,3±3,1	21,0±3,7	19,7±3,2	13,9±2,0	14,1±5,0
LF/HF	1,32±0,1	1,23±0,4	1,23±0,7*	0,96±0,1	0,81±0,1	1,1±0,3	1,21±0,05	1,2±0,1
IC	5,2±0,8*	2,8±1,0	3,0±0,07*	1,7±0,5	2,4±0,2	2,3±0,1	2,6±0,7	2,4±0,7
MFI	1,8±0,1*	1,3±0,3	0,97±0,2	0,81±0,4	2,05±0,05	1,81±0,4	0,98±0,1*	0,54±0,1

Table 3: Dynamics of indices of vegetative regulation of patients with diabetes with CAS in the course of treatment with ACE inhibitors.
Group A – Patients with unsatisfactory compensation of diabetes (HbA1c≥7,5%); Group B - patients with satisfactory compensation of diabetes (HbA1c<7,5%); IC - index of centralization; MFI – morpho-physiological index; * - p < 0,05
1 - study prior to initiation of therapy with capillary; 2 - study after the course of therapy.

In patients with type 1 diabetes, with an inadequate compensation, the increase in sympathetic activity led to compensatory tension in the parasympathetic section of the autonomic nervous system. The tension of the adaptation mechanisms was inadequate to the growth of functioning. "A" type 1 diabetes was less than in gr. "B", which is indicative, rather than an increase in sympathetic activity, and a decrease in vegetative influences in regulating heart rate and unsatisfactory adaptation.

Adverse events

During the study, no adverse events were noted.

Discussion

Unsatisfactory compensation of diabetes mellitus is accompanied by significant changes in the parameters of heart rate variability (HRV), but the direction and severity of disorders in patients with different types of diabetes is not the same. We managed to prove that in patients with type 1 and type 2 diabetes with cardiac autonomic neuropathy, multidirectional types of vegetative reactions accompany decompensation. Thus, the circadian index in patients with type 2 diabetes was very low – 1.19 ± 0.08, which is possible only with a marked violation of the central and vegetative regulating the heart rate. The power of the low-frequency spectrum (LF-24.2 ± 2.1%, VLF-23.4 ± 1.7%, ULF-30.8 ± 8.4%) prevailed over the high-frequency power (HF-21.6 ± 2.9%), which is typical for pronounced vegetopathy and failure of vegetative regulation. At the same time the age of the patient and the length of diabetes were of no fundamental importance. Unsatisfactory compensation for type 1 diabetes did not affect CI (1.32 ± 0.17), but was accompanied by a decrease in the total spectrum power (TC 1675.2 ± 233.4 ms^2), the predominance of low-frequency spectrum power (ULF-36.5 ± 11.0%, VLF-33.9 ± 4.7%, LF-17.4 ± 6.9%) over the high-frequency (HF-11.7 ± 1.5%). The coefficient of the vagetative sympathetic balance of patients with type 1 diabetes on the background of decompensation (LF/HF) was above the average of 1.58 ± 0.4, confirming hyper sympathetic tone. In patients with type 2 diabetes, decompensation of diabetes, also accompanied by vegetative imbalance, but proceeded against the background of increased activity of the parasympathetic nervous system (LF/HF = 0.86 ± 0.07). The obtained data showed that the presence of cardiac autonomic neuropathy, even against a background of satisfactory compensation of diabetes, leads to high activity of the central energy-consuming mechanisms, to a violation of vegetative regulation, and the state of subcompensation was provided by the stress of humoral metabolic processes.

A number of indices for the rehabilitation of adverse prognosis (MFI≥1) patients with DT1- TC <1500 ms² (RR = 2,5), VLF <50% in the structure of the spectrum (RR = 1.46), LF/HF ≥3.0 (RR=1.77), IC ≥3.50 (RR = 3.52), the index of regulatory systems tension (RR = 3.1). In patients with DT2, symptoms of autonomic dysfunction are observed with the onset of the disease.

The state of unsatisfactory adaptation is characterized by an increase in the degree of tension of regulatory systems and a decrease in the functional reserve. With the disruption of adaptation, which is the case in patients with diabetes mellitus, there is a sharp decline in the level of functioning of the system as a result of depletion of regulatory systems.

When compensating for type 1 diabetes, homeostasis was preserved through the activation of energy mechanisms-an increase in the tone of the sympathetic nervous system was accompanied by an increase in heart rate. The presented data show that the severity of hyper sympathetic tone was determined by compensation of diabetes. The purpose of the ACE inhibitor for decompensation of type 1 diabetes and the presence of CAS did not significantly affect vegetative imbalance, but in patients with compensated course of DM changes in the orientation of vegetative reactions approaching the age norm. The predominance of parasympathetic nervous system activity is characteristic of healthy people for 4 decades of life. The activity of central regulatory mechanisms decreased (decrease in VLF, IC), adaptation voltage (MFI <1).

In type 2 diabetes, the predominance of parasympathetic activity under decompensation conditions increased HF and LF simultaneously. The appointment of ACE inhibitors in patients with CAS and type 2 diabetes with decompensation did not significantly affect the vegetative balance. The efficacy of Ramipril monotherapy in this group of patients also raised doubts that we associated with the effects of bradykinin in hyper parasympathetic tone. Treatment with ramipril in patients with compensated course of type 2 diabetes promoted a decrease in activity of central humoral-metabolic processes of regulation of heart rhythm (decrease in VLF) and tension of adaptation mechanisms (MFI = 0.54 ± 0.1).

Conclusion

The lack of indicators characteristic of the unfavorable rehabilitation prediction (MFI≥1) of patients with DT1, we classified: TC less than 1500 мс² (RR=2.5; CI 95%=1.4-3.6), VLF более 50% Spectrum structure (RR=1.46; CI 95%=1.0-2.9), ULF (RR=1.58; CI 95%=0.8-2.02) LF/HF ≥3,0 (RR=1.77; CI 95% =1.02-3.06), ИЦ ≥3.50 (RR = 3.52; CI 95% =1.35-4.22), IVR (RR = 2.7; CI 95%=1.5-3.5). The voltage index of regulatory systems IN (RR = 3.1; CI 95% = 1.56-4.55). In patients with type 2 DM, signs of vegetative dysfunction are observed from the onset of the disease and accompany the development of the process constantly. Among the indices typical for an unfavorable rehabilitation prognosis of patients with type 2 diabetes we attributed CI ≤1,0 (RR = 1.74; CI 95% = 1.21-2.67), IC ≥ 3,50 (RR=3.1; CI 95% =1.12-4.1), IVR (RR =2.5; CI 95% = 1.35-3.15), IN (RR = 2.8; CI 95% =1.53-4.32).

Authors' Contributions

Irina Kurnikova was a major contributor in writing the manuscript, and analyzed and interpreted the data of patients. Guzal Ahmadullina participated in the examination of patients and collection of material. Ramchandra Sargar contributed to manuscript preparation. All authors read and approved the final manuscript.

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