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Research Article

Diabetic Autonomic Cardiac Neuropathy and The Effectiveness of Anti-Hypertensive Therapy

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Abstract

Background: Cardiac form of diabetic autonomic neuropathy (DAN) leads to the impairment of autonomic regulation of the body and changes the parameters of heart rate variability. This article is trying to answer to the underlying issue like the influence of cardiac autonomic neuropathy and the efficacy of administered angiotensin converting enzyme (ACE) inhibitors in decompensated diabetes mellitus (DM).

Methods: A total of 35 patients of diabetes mellitus 1 and 2 were recruited. The general clinical laboratory tests and spectral parameters of daily heart rate monitoring were done in the inpatient department.

Results: Compensatory hyperactivation of the parasympathetic system (PNS) of autonomic nervous system (ANS) and centralization of regulatory processes were observed in patients with decompensated DM type 1. The administration of ACE inhibitors in these cases had a positive effect not only on myocardial hemodynamic parameters, but also restored the autonomic balance. The predominance of parasympathetic activity has been observed in patients with decompensated DM type 2. However, the administration of ACE inhibitors did not affect on the autonomic balance but after reaching the target values of glycemic control, the administration of ACE inhibitors led to the achievement of not only a hypotensive effect, but also to a decrease in the manifestations of autonomic dysfunction.

Conclusions: Cardiac autonomic neuropathy (CAN) results in autonomic dysfunction and prompts the body to activate central (energy-consuming) regulation mechanisms. The administration of ACE inhibitors in diabetic patients had a positive effect on the parameters of autonomic regulation in patients with type 1 diabetes and the hypotensive effect was higher in patients with compensated type 2 diabetes.

Keywords: Diabetes Mellitus (DM); Cardiac Autonomic Neuropathy (CAN); Heart Rate Variability (HRV); Hypotensive Drugs

Introduction

The manifestation of diabetic neuropathy is often encountered during the process of development and progression of diabetes. The damages of nervous system occur simultaneously at all the levels and classified clinically as peripheral, central and autonomic neuropathy. However, the signs of diabetic autonomic neuropathy (DAN) accounts for 3.5 - 6.0% of patients at the onset of disease and 100% in patients with a longer course [1-4]. The onset of autonomic neuropathy changes the course and prognosis of diabetes. There are such changes as the absence of clinical signs of hypoglycemia and counter regulation functions, impaired absorption of carbohydrates in the gastrointestinal tract, changes in the bioavailability of oral hypoglycemic drugs and other drugs, the rapid progression of micro- and macrovascular complications, the formation of osteoarthropathy and ulcerative defects.

According to literature reviews, after the clinical manifestation of CAN, the mortality rate of patients of this group in the next five years increases up to 35 - 50% [5,6]. It should be noted that CAN is by far the most studied form of autonomic neuropathy in diabetic patients, but this diagnosis is made to only after the exclusion of

other causes leading to complaints and symptoms from the cardiovascular system or in the later stages after the formation of a fixed heart rate.

Clinical signs and symptoms of CAN are cardiac arrhythmias, formation of a 'fixed heart rate', poor response to drugs, reduced variation in R-R intervals, an increase in sensitivity to catecholamines (arrhythmia, asystole), a labile course of diabetes (a sharp decrease in residual insulin secretion), orthostatic hypotension and arterial hypertension in a horizontal position, negative orthostatic test, decrease in coefficient 30/15.

However, ANS is one of the most significant regulatory systems and ensures the functioning of the body. Autonomic dysfunction, developed on the background of CAN, leads to dysregulation of the heart rhythm. The impairment of heart rate variability (HRV) in diabetic patients is well known [7,8]. It has been more than 20 years since the research was started and identified not only the dependence between the impairment of HRV regulation, progressive DM and also the impaction of this impairment on the rate of formation and progression of vascular complications [9].

An important section of this research was to study the efficacy of hypotensive and antihypertensives drugs in diabetic patients with CAN and the impact of the impaired autonomic regulatory mechanism on the prognostic effect on this drugs. ACE inhibitor was the treatment of choice for this investigation. ACE inhibitors are widely used as a treatment in DM for the prevention of the progression of macrovascular complications [10]. After the completion of the HOPE study (the effectiveness of ramipril in the prevention of cardiovascular complications in 3577 patients with diabetes - MICRO-HOPE), this drug is prescribed much more often [11]. According to this study, ramipril therapy reduced the risk of myocardial infarction by 22%, stroke by 33%, cardiovascular death by 37%, death from any cause by 24%, revascularization by 17% and nephropathy by 24%. The protective effect of ramipril on blood vessels and kidneys was revealed in patients with diabetes. The data obtained allowed ramipril to be prescribed to patients with diabetes even in the absence of diabetic nephropathy or arterial hypertension, which are standard indications for the use of ACE inhibitors in such patients [11]. The more attention was paid to practical recommendation of ACE inhibitors in diabetic patients with the impaired autonomic regulation and the influence of disease compensation on the effectiveness of therapy.

Aims

To study of the relationship of heart rate variability in patients with diabetes complicated by cardiac autonomic neuropathy (CAN) and the effectiveness of antihypertensives therapy (Ramipril) depending on the type and compensation of diabetes.

Materials and Methods

The study was conducted during 2010-2015y.y. based on Endocrinology department of the regional clinical Hospital (Izhevsk, Russia) and Endocrinology Department of City Clinical "A.K. Eramishantsev" Hospital (Moscow, Russia).

The study design did not contemplate a comparison of the effectiveness of antihypertensive drugs with each other, but a comparison of the effectiveness of the same drug in different conditions of the disease. The control of carbohydrate metabolism was ensured according with the recommendations of WHO / IDF [12] by repeated studies of the glycemic profile and glycated hemoglobin (HbA1c).

Diagnostic method for CAN was the assessment of 24-h HRV by Holter monitoring with "VALENTA" device (Table 1). This device is equipped with a program for computer processing of spectral analysis parameters: total spectrum power (TP), high-frequency (HF), low-frequency (LF), very-low-frequency (VLF), ultra-low-frequency (ULF) bands, ratio of LF-to-HF power% (LF/HF), relative power of the High-frequency% (HF%), relative power of the low-frequency band% (LF%), relative power of the very-low-frequency VLF (%), relative power of the ultra-low-frequency ULF (%), CI (Centralization Index). Assessment of general parameters: standard deviation of RR intervals (SDRR), Standard deviation of the average NN intervals for each 5 min segment of a 24 h HRV recording (SDARR), percentage of successive RR intervals that differ by more than 50 ms (pNN50).

ECG was recorded in all patients in 1 - 5 modified chest leads within 24 hours. During the examination, the patient has recorded their data in a "DIARY". Subsequent analysis was carried out automatically in comparison with the physical and other activity of the patient [13].

Parameters	Unit	Description
TP	ms^2	Total spectrum power band (0.003 to 0.40 Hz)
ULF	ms^2	Ultra-low-frequency band (≤0,0033 Hz)
VLF	ms^2	Absolute power of the very-low-frequency band (0.0033–0.04 Hz)
LF power	ms^2	Absolute power of the low-frequency band (0.04–0.15 Hz)
HF power	ms^2	Absolute power of the high-frequency band (0.15–0.4 Hz)
LF/HF	%	Ratio of LF-to-HF power
SDRR	ms	Standard deviation of RR intervals
SDARR	ms	Standard deviation of the average NN intervals for each 5 min segment of a 24 h HRV recording
pNN50	%	Percentage of successive RR intervals that differ by more than 50 ms

Table 1: Following parameters of frequency-domain were measured.

Study object

The examination of parameters of autonomic regulation has been conducted in 19 patients with DM 1 (aged 37.1 ± 6.4yrs) and 26 patients with DM 2 (aged 54.3 ± 5.9yrs). All groups have been surveyed depending on the metabolic parameters of compensated diabetes. All patients have been administered Ramipril 1.25 - 2.5 mg once a day as the main antihypertensive drug. In the study groups, the prescribed dose was sufficient to achieve a therapeutic effect.

Results

A low count of all parameters of general analysis was reported relative to the normal values in spite of compensated DM. Decompensated DM influenced indirectly on the average values of parameters, underlying the internal relationship of autonomic and metabolic disorders. The presented data are typical for patients with CAN (Table 2 and 3). CAN has been established not only by average analysis in groups but also by individual parameters of general analysis of HRV.

A low count of all parameters of general analysis was reported relative to the normal values in spite of compensated DM. Decompensated DM influenced indirectly on the average values of parameters, underlying the internal relationship of autonomic and metabolic disorders. The presented data are typical for patients with CAN (Table 2 and 3). CAN has been established not only by average analysis in groups but also by individual parameters of general analysis of HRV.

Patient's total spectrum power band (TP) was increased as compare to normal value (3446 ± 1018ms2) on the background of decompensated and compensated DM. The increased TP in decompensated DM suggest about adaption response to stress was on the background of preserved autonomic regulation mechanism (ULF decreased). Absolute power of the very-low-frequency band (VLF) increased in poorly compensated DM, which reflected the involvement of central (suprasegmental) ergo tropic and humoral-metabolic mechanisms in the regulation of heart rhythm (see Table 3).

Parameters	DM type 1 (n=19)		DM type 2 (n=26)		Normal values	
	Group. A (n=11)	Group. B (n=8)	Group. A (n=14)	Group. B (n=12)	30-39 yrs	50-59 yrs
CI	132,5 ± 44,1*	128,1 ± 21,8	119,3 ± 28,6*	127,8 ± 12,0	1,32 ± 0,178 ± 7	1,32 ± 0,176,9
Avg.HR in day	83,7 ± 12,8*	88,1 ± 19,1	82,6 ± 7,4	84,1 ± 4,9	-	-
Avg.HR in night	63,1 ± 3,9	68,9 ± 6,1	69,5 ± 2,8	66,6 ± 3,1	143 ± 32	121 ± 27
SDRR 24hrs	41,1 ± 11,1*	20,4 ± 9,0	65,0 ± 8,7*	31,7 ± 4,9	-	-
SDRR day	28,9 ± 5,7	20,3 ± 7,2	41,3 ± 3,1*	31,0 ± 3,8	-	-
SDRR night	16,1 ± 6,7*	20,4 ± 4,6	34,2 ± 1,9	32,0 ± 3,2	130 ± 33	106 ± 27
SDARR 24hrs	53,0 ± 13,4*	42,6 ± 4,9	77,4 ± 15,1*	57,9 ± 11,3	-	-
SDARR day	63,7 ± 10,0*	38,7 ± 11,0	83,4 ± 21,0*	55,0 ± 12,7	-	-
SDARR night	70,6 ± 9,3*	45,7 ± 10,2	72,9 ± 18,0*	60,3 ± 9,1	13 ± ´	6 ± 6
pNN50%24hrs	8,2 ± 1,1*	6,5 ± 0,7	6,5 ± 1,4	5,5 ± 0,9	-	-
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 2: General analysis of HRV.

Group.A – Patients with decompensated DM; Group.B – Patients with compensated DM; CI- circadian index; HR- heart rate. * - p < 0,05.

Parameters	DM type 1 (n=19)		DM type 2 (n=26)	
	Group. A (n=11)	Group. B (n=8)	Group. A (n=14)	Group. B (n=12)
CI	132,5 ± 44,1*	128,1 ± 21,8	119,3 ± 28,6*	127,8 ± 12,0
Avg.HR in day	83,7 ± 12,8*	88,1 ± 19,1	82,6 ± 7,4	84,1 ± 4,9
Avg.HR in night	63,1 ± 7,9	68,9 ± 8,1	69,5 ± 2,8	66,6 ± 3,1
HR Min day.	54,2 ± 1,7*	61,6 ± 2,3	59,1 ± 2,9	57,7 ± 3,2
HR Max day.	129,3 ± 13,1*	137,4 ± 9,9	131,8 ± 7,1	128,6 ± 13,0
TP (ms^2)	8741,6 ± 112,7	7824,4 ± 139,4	7433,4 ± 212,3*	5274,5 ± 149,8
ULF (%)	35,3 ± 3,7*	42,6 ± 2,5	32,1 ± 2,9*	50,7 ± 4,4
ULF (ms^2)	1987,0 ± 118,6*	2750,1 ± 211,1	1684,5 ± 143,5	2266,3 ± 148,0
VLF (%)	39,3 ± 4,9*	25,6 ± 2,8	24,6 ± 2,5	23,4 ± 3,3
VLF (ms^2)	4394,5 ± 312,1*	1940,5 ± 159,0	2491,5 ± 165,3*	1354,0 ± 117,9
LF (%)	14,6 ± 3,3*	17,5 ± 5,1	25,3 ± 4,7*	12,4 ± 1,9
LF (ms^2)	1456,0 ± 137,3	1684,8 ± 159,6	1542,7 ± 201,0*	895,4 ± 79,8
HF (%)	10,35 ± 2,1*	14,2 ± 1,8	21,0 ± 3,7*	13,9 ± 2,0
HF (ms^2)	1104,1 ± 58,8*	1604,2 ± 117,1	1629,7 ± 131,2*	759,3 ± 48,9
LF/HF	1,32 ± 0,1	1,225 ± 0,7	0,81 ± 0,1*	1,21 ± 0,05
IC	5,2 ± 0,8	3,0 ± 0,07	2,4 ± 0,2	2,6 ± 0,7

Table 3: Spectral analysis of HRV.

Group.A – Patients with decompensated DM; Group.B – Patients with compensated DM * - $p < 0,05$

IC- index of centralization; CI- circadian index.

In patients with decompensated type 1 DM, absolute power of the high and low-frequency (HF, LF) was decreased and increased the activity of the central circuit of regulation (increased IC), the tone of the ANS showed a predominance of sympathetic activity (increased LF / HF). In patients with decompensated type 2 DM, increased absolute power of the high and low-frequency (HF, LF) was associated with the predominance of parasympathetic activity (decreased LF / HF). The administration of ACE inhibitor influenced on not only myocardial hemodynamic parameters, but also the autonomic equilibrium of diabetic patients with CAN. (Table 4).

	Type 1 DM (n=19)				Type 2 DM (n=26)			
	Group. A (n=11)		Group. B (n=8)		Group. A (n=14)		Group. B (n=12)	
	1	2	1	2	1	2	1	2
TP(ms^2)	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

Table 4: Dynamics of parameters of autonomic regulation of diabetic patients with CAN during treatment with ACE inhibitors.

Group.A – Patients with decompensated DM; Group.B – Patients with compensated DM * 1 - study before starting ramipril therapy; 2 - study after a course of ramipril therapy. * $p < 0,05$. IC- index of centralization.

In patients with poorly compensated type 1 DM, increased sympathetic activity led to compensatory stress in the parasympathetic system of ANS. The stress of the adaptation mechanisms was inadequate to the functioning growth. The heart rate was lower in group 'A' type DM than group 'B', which suggest not about increased sympathetic activity rather about decreased autonomic influences on the regulation of heart rate and poor adaptation. There is an abrupt decrease in the level of the functional system as a result of depletion of regulatory systems in diabetic patients, which is associated with the failure of adaptation.

Homeostasis on the background of compensated type 1DM persisted by means of the activated energy mechanism and hyperactivity of SNS was accompanied by an increased HR. The data presented in Table 2 suggest that the severity of hyperactivity of SNS was determined by compensated DM. The administration of ACE inhibitors in poorly compensated type 1DM in patients with CAN have no significant impact on autonomic disbalance, however, changed the direction of autonomic reactions (see Table 4) by approaching the normal age in patients with compensated DM. The predominance of the activity of PNS is characteristic of healthy people in the fourth decade of life. The activity of central regulatory mechanisms decreased (VLF, IC).

The predominance of parasympathetic activity contributed to an increase in HF and LF simultaneously in decompensated type 2 DM (see Table 3). The administration of 'Ramipril' in decompensated type 1DM in patients with CAN have no significant impact on autonomic disbalance. The efficacy of 'Ramipril' monotherapy in this group of patients also raised questions, which was associated with the effects of bradykinin in hyper parasympathetic activity (see Table 3). Treatment with 'Ramipril' contributed to a decrease in the activity of the central humoral-metabolic processes of heart rate regulation (decreased VLF) in compensated type 2 DM patients.

Conclusion

The obtained data showed that the presence of CAN, regardless of the quality of compensation for diabetes, leads to a high activity level of central energy-consuming mechanisms, impaired autonomic regulation, and the achievement of compensation was ensured by high exerting of the humoral-metabolic processes. Moreover, we managed to establish that an increase in VLF in the structure of the HRV power spectrum in patients with diabetes complicated by cardiac autonomic neuropathy is an indication for the appointment of an ACE inhibitor. We do not claim that the identified effects of ramipril in patients with diabetes and CAN belong to the class of ACE inhibitors in general, since this requires additional analysis.

In patients with satisfactory compensation for type 1 diabetes and CAN, ramipril had a positive effect not only on myocardial hemodynamic parameters, but also on indicators of the autonomic regulation of heart rhythm. Compensation of type 2 diabetes in patients with CAN is a prerequisite for achieving the therapeutic effect of ramipril in a monovariant.

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Bibliography

1. Dimitropoulos G., *et al.* "Cardiac autonomic neuropathy in patients with diabetes mellitus". *World Journal of Diabetes* 5.1 (2014): 17-39.

2. Rodica Pop-Busui and Andrew JM. "Diabetic Neuropathy: A Position Statement by the American Diabetes Association". *Diabetes Care* 40 (2017): 136-154.

3. Vinik AI., *et al.* "Diabetic autonomic neuropathy". *Diabetes Care* 26.5 (2003):1553-1579.

4. Vinik AI., *et al.* "Autonomic imbalance: prophet of doom or scope for hope?". *Diabetic Medicine* 28 (2011): 643-651.

5. Maser RE., *et al.* "The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes: a meta-analysis". *Diabetes Care* 26 (2003): 1895-1901.

6. Ludka O., *et al.* "Sleep apnea, cardiac arrhythmias, and sudden death". *Texas Heart Institute Journal* 38 (2011): 340-343.

7. Pavy-Le Traon A., *et al.* "Cardiovascular autonomic neuropathy and other complications in type 1 diabetes". *Clinical Autonomic Research* 20 (2010): 153-160.

8. Tang ZH., *et al.* "Association and predictive value analysis for resting heart rate and diabetes mellitus on cardiovascular autonomic neuropathy in general population". *Journal of Diabetes Research* (2014): 215473.

9. Kurnikova IA., *et al.* "Autonomic neuropathy in the development and progression of vascular complications of diabetes mellitus". *Neurology and Neuroscience Reports* 11.1.2 (2018): 1-5.

10. Yusuf S. "Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients". The Heart Outcomes Prevention Evaluation Study Investigators *The New England Journal of Medicine* 342 (2000): 145-153.

11. The Heart Outcomes Prevention Evaluation Study Investigators. "Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy". *Lancet* 355 (2000): 253-259.

12. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia". Report of WHO/IDF Consultation (2006).

13. Heart Rate Variability. Standarts of Measurements physiological Interpretation and Clinical Use (1996).

Volume 3 Issue 12 December 2019