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Вариабельность артериального давления и ритма сердца у больных с ишемической болезнью сердца и сахарным диабетом, влияние ингибитора натрийглюкозного ко-транспортера 2 типа

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АННОТАЦИЯ

Введение. Фактором, усугубляющим течение ишемической болезни сердца (ИБС) у больных сахарного диабета 2 типа (СД2), является кардиоваскулярная автономная нейропатия (КАН), при которой в 5 раз увеличивается риск внезапной смерти. Распространенность КАН у больных ИБС в сочетании с СД2 может достигать 60%. Классические кардиоваскулярные тесты (ККТ) не позволяют выявлять КАН на доклинической стадии. Современным методом лечения СД2 являются ингибиторы натрийглюкозного ко-транспортера 2 типа, доказавшие кардиопротективные эффекты.

Цель. Анализ распространенности изменений вариабельности артериального давления (ВАД) и ритма сердца (ВРС) у больных ИБС в сочетании с СД2 и влияния эмпаглифлозина на эти параметры.

Материалы и методы. Обследовано 210 пациентов 64,5 ± 6,7 лет (103 мужчины) с ИБС в сочетании с СД2 (1 группа). Анализировались антропометрические и биохимических показатели, проведено суточное мониторирование электрокардиограммы и артериального давления, выполнены ККТ. Для сравнения обследовано 64 пациента с ИБС, не имеющих нарушений углеводного обмена (2 группа, n = 64, 66,4 ± 2,3 лет). Далее из числа обследованных пациентов 1-ой группы отобраны пациенты (n = 42) с нарушениями ВРС и ВАД, но суммой баллов ККТ < 4,0; они разделены на группу 1Г (n = 22) — добавлен эмпаглифлозин 10–25 мг в сутки — и 1С (n = 20) — продолжили ранее проводимую терапию.

Результаты. У 22% пациентов с ИБС в сочетании с СД2 выявлена КАН, все они имели нарушения ВРС и ВАД. Отклонения показателей ВРС и ВАД при нормальной сумме баллов ККТ (<4,0) выявлены у 43% больных. В течение 6 мес. лечения эмпаглифлозином уровень HbA1c снизился с 8,38 ± 0,56 % до 6,9 ± 0,26% (p < 0,05), в группе без эмпаглифлозина - с 8,28 ± 0,32% до 7,30 ± 0,29% (p < 0,05). В группе эмпаглифлозина средняя ЧСС за сутки снизилась с 86,7 ± 2,4 уд./мин до 76,7 ± 2,1 уд./мин (p < 0,05), циркадный индекс увеличился с 1,19 ± 0,02 до 1,30 ± 0,01 (P < 0,05), SDNN увеличился с 106,1 ± 2,21 до 114,03 ± 2,34 мс (p < 0,05), индекс вариабельности систолического артериального давления (САД) днем снизился с 22,9 ± 1,7 до 16,4 ± 1,9 %, p < 0,05, САД ночью — с 16,8 ± 2,2 до 12,3 ± 2,6%, p < 0,05.

Заключение. Выявляемые изменения показателей ВРС и ВАД могут быть проявлением КАН и при сумме баллов ККТ < 4,0 свидетельствовать о ее доклинической стадии. Зарегистрирована положительная динамика ВРС и ВАД на фоне лечения эмпаглифлозином, продемонстрировавшим его способность улучшать функциональное состояние вегетативной нервной системы.

Ключевые слова: *ишемическая болезнь сердца; ИБС; сахарный диабет; автономная нейропатия; вариабельность ритма сердца; вариабельность артериального давления; эмпаглифлозин*

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Variability of arterial pressure and cardiac rhythm in patients with coronary heart disease and diabetes mellitus: Effect of sodium-glucose co-transporter 2 inhibitor

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ABSTRACT

INTRODUCTION: A factor that worsens the course of coronary heart disease (CHD) in patients with type 2 diabetes mellitus (DM2) is cardiovascular autonomic neuropathy (CAN), in which the risk of sudden death increases fivefold. The prevalence of CAN in patients with both CHD and DM2 may reach 60%. Classic cardiovascular tests (CCT) do not permit identification of CAN at the preclinical stage. A modern method of treatment for DM2 uses sodium-glucose co-transporter 2 inhibitors, which have confirmed cardioprotective effects.

AIM: To analyze the prevalence of alterations of arterial pressure variability (APV) and of heart rhythm variability (HRV) in patients with both CHD and DM2 and the effect of empagliflozin on these parameters.

MATERIALS AND METHODS: A total of 210 patients aged 64.5 ± 6.7 years (103 men) with both CHD and DM2 were examined (group 1). Anthropometric and biochemical parameters were analyzed, electrocardiogram and arterial pressure were monitored daily, and CCT was performed. For comparison, 64 patients with CHD with no alterations in the carbohydrate metabolism were examined (group 2, n = 64, aged 66.4 ± 2.3 years). Further, among patients in group 1, patients with impaired HRV and APV were selected, but they had CCT scores < 4.0, and they were divided into group 1G (n = 22) where empagliflozin was added (10–25 mg/day) and group 1C (n = 20) where the previous therapy was continued.

RESULTS: CAN was detected in 22% of patients with CHD and DM2, and all patients had impaired HRV and ADV. Deviations of HRV and APV parameters with normal CCT scores (< 4.0) were detected in 43% of the patients. Within 6 months of treatment with empagliflozin, the HbA1c level decreased from 8.38% ± 0.56% to 6.9% ± 0.26% ($p < 0.05$); in the group without empagliflozin treatment, it decreased from 8.28% ± 0.32% to 7.30% ± 0.29% ($p < 0.05$). In the empagliflozin group, the average heart rate per day decreased from 86.7 ± 2.4 to 76.7 ± 2.1 beats/min ($p < 0.05$), the circadian index increased from 1.19 ± 0.02 to 1.30 ± 0.01 ($p < 0.05$), the SDNN increased from 106.1 ± 2.21 to 114.03 ± 2.34 ms ($p < 0.05$), and the systolic arterial pressure variability index decreased from 22.9% ± 1.7% to 16.4% ± 1.9% at daytime ($p < 0.05$) and from 16.8% ± 2.2% to 12.3% ± 2.6% at nighttime ($p < 0.05$).

CONCLUSION: The identified alterations of HRV and APV parameters may be manifestations of CAN, and CCT score < 4.0 may indicate the preclinical stage. Positive dynamics of HRV and APV was recorded with empagliflozin therapy, which improved the functional condition of the autonomic nervous system.

Keywords: *coronary heart disease; CHD; diabetes mellitus; autonomic neuropathy; heart rate variability; arterial pressure variability; empagliflozin*

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ECO•VECTOR

LIST OF ABBREVIATIONS

APV — arterial pressure variability
HRV — heart rate variability
RRCH — Rostov Regional Clinical Hospital
DAPd — daytime diastolic arterial pressure
DAPn — nighttime diastolic arterial pressure
CHD — coronary heart disease
SGLT-2 — sodium-glucose linked transporter-2 inhibitor
CAN — a cardiovascular form of diabetic autonomic neuropathy
CCT — classic cardiovascular test
SAPd — daytime systolic arterial pressure
SAPn — nighttime systolic arterial pressure
DM2 — type 2 diabetes mellitus
24HAPM — 24-hour arterial pressure monitoring
24HECGM — 24-hour electroencephalogram monitoring
CI — circadian index
HR — heart rate
pNN50 — the percentage of adjacent NN intervals differing by >50 ms
RMSSD — root mean square of the sum of differences of successive R-R intervals
SDNN — standard deviation of all R-R intervals

INTRODUCTION

The interrelation between type 2 diabetes mellitus (DM2) and coronary heart disease (CHD) is out of doubt [1]. It is not by chance that DM2 modern treatment implies multifactor control-directed not only to normalize hyperglycemia but also prevent CHD development and progression [2]. An important factor that aggravates the course of CHD is the cardiovascular form of diabetic autonomic neuropathy (CAN), which increases the risk of death by 5-folds [3, 4]. Information on CAN prevalence remains ambiguous up to the present moment, and according to different studies, it ranges from 25% to 60% [5, 6]. The significant clinical manifestations of CAN include disorders in the variability of the heart rhythm (HRV) and arterial pressure (APV) that may be identified in classic cardiovascular tests (CCT) according to D. Ewing [6].

Unfortunately, CCT permits the identification of CAN at the stage of clinical manifestations. Concurrently, no sufficient information is available about the preclinical stage diagnosis of CAN, although alterations in the autonomic nervous system at the preclinical stage are known to be reversible [5, 7].

In recent years, special attention in DM2 treatment has been given to sodium-glucose-linked transporter-2 inhibitors (iSGLT-2), which have proven several cardioprotective effects and cardiorenal outcome improvements [9–11]. Here, a probable effect of iSGLT-2 on the myocardium, myocardial energetics and metabolism [11, 12], stiffness of the vessel wall, natriuresis, and osmotic diuresis [10] is discussed, as well as a probable hypervolemia reduction due to the interstitial fluid [10–12]. Additionally, the authors did not encounter any related literature that investigated the effect of iSGLT-2 on the functional condition of the autonomic nervous system, impaired HRV, and APV.

Aim — analyze the prevalence of alterations APV and HRV in patients with CHD in combination with DM2 and the effects of empagliflozin on these parameters.

MATERIALS AND METHODS

The study was conducted on the clinical base of Rostov Regional Clinical Hospital (RRCH) and was approved by the Ethics Committee of Rostov State Medical University (Protocol of the meeting No. 15/18 of 11.10.2018).

To realize the set aim, in the first stage examined 210 patients with CHD in combination with DM2 (***group 1***) who underwent treatment in the cardiologic unit of RRCH. Of them, 107 (50.4%) were females and 103 (49.5%) were males, with a mean age of 64.5 ± 6.7 years.

In all patients, anthropometric parameters were analyzed, and biochemical examination results were evaluated, including plasma glucose in fasting condition and 2 h after a meal, HbA1c, blood lipid spectrum parameters, C-peptide, and immunoreactive insulin with Homeostatic model assessment insulin resistance index calculation. Instrumental research methods included:

1) 24-h monitoring of electroencephalogram (24HECGM) with the determination of the average heart rate (HR, beat/min) per day, circadian index (CI), and the time characteristics of HRV as the following:

- standard deviation of all R-R intervals (SDNN, ms),

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- square root of the sum of differences of sequential R-R intervals (RMSSD, ms),

- the percentage of adjacent NN intervals differing by >50 ms (pNN50, %).

2) 24-h monitoring of arterial pressure (24HAP) with the calculation of variability indices;

- daytime and nighttime systolic arterial pressure (SAPd, % and SAPn, % respectively),

- daytime and nighttime diastolic arterial pressure (DAPd, % and DAPn, % respectively).

CHD diagnosis was confirmed by the coronarography (CG) results. In the group with CHD without DM2, monovascular lesions of the coronary vessels were more commonly identified (74% vs. 12%, $p < 0.05$), and contrarily, multisegmental lesions of the coronary vessels were identified in those with DM2. In group 1 (CHD + DM2), more cases of hemodynamically significant stenoses were found (79% vs. 56%, $p < 0.05$).

CAN was verified based on the CCT assessment.

For comparison, 64 patients with CHD without carbohydrate metabolism disorders (***group 2***) were examined. In the study groups, the number of males and females were similar (Table 1), as well as the age of patients, and blood pressure was equally elevated. As expected, the groups differed in body mass index (BMI) and HbA1c. No significant differences were found in the lipid spectrum, except triglycerides that were higher in group 1.

Table 1. Comparative Analysis of Clinical and Demographic Characteristics of Patients of the Study Groups

Parameter	Group 1	Group 2	p
n	210	64	
Age, years	64.2 ± 3.1	66.4 ± 2.3	>0.1
Body mass index, kg/m^2	33.8 ± 2.3	27.2 ± 2.5	***<0.05***
HbA1c, %	8.28 ± 0.87	5.28 ± 0.22	***<0.01***
High density lipoprotein cholesterol, mmol/l	0.92 ± 0.46	1.21 ± 0.34	>0.1
Low density lipoprotein cholesterol, mmol/l	2.53 ±1.76	2.28 ± 1.49	>0.1
Triglycerides, mmol/l	2.96 ± 0.75	1.17 ± 0.50	***<0.05***
C-peptide, pmol/l	625.1 ± 82.6	563.5 ± 23.6	>0.1
Immunoreactive insulin, μIU/ml	12.6 ± 1.34	6.43 ± 0.65	***<0.05***
HOMA insulin resistance index	6.76 ± 0.77	2.16 ± 0.28	***<0.05***

In the second stage of the study, 42 patients were isolated from group 1 (CHD + DM2) with HRV and APV disorders (CI < 1.24, SAPd > 20%, SAPn > 10%, DAPd > 15%, DAPn > 10%), but the total score of CCT (<4.0) evidenced the absence of the clinical stage of CAN.

All patients with DM received combined hypoglycemic therapy, which included metformin, preparations of sulfonylurea, and basal analogs of human insulin, but the target values of carbohydrate metabolism were not achieved (HbA1c > 8.0%). From this cohort of patients, 2 groups were isolated: 1G group (n = 22), wherein iSGLT-2 empagliflozin of 10–25 mg per day was added to the combination therapy to improve carbohydrate metabolism, and 1C group (n = 20), who continued the previously conducted therapy.

Control examinations of patients and corrections of doses of preparation were conducted monthly until the level of HbA1c of <7.5% was achieved. To assess the dynamics of the studied HRV and APV parameters after 6 months, 24HECGM, 24HADM, and CCT were repeatedly performed. Patients of 1G and 1C groups additionally filled out a specially designed questionnaire to assess the dynamics of clinical manifestations of CHD, body weight, hypoglycemic conditions, and quality of life parameters.

The study excluded patients with myocardial infarction or stroke that previously occurred in <3 months, severe liver and kidney pathology, oncological diseases, stages III and/or IV functional class chronic heart failure, and severe hypoglycemic conditions (requiring the help of another person, with or without loss of consciousness) within the previous 3 months.

Statistical analysis of the data was performed using Microsoft Office Excel 2010 (Microsoft Corp., USA) and STATISTICA 10.0 (Stat Soft Inc., USA) software. The type of data distribution was assessed using the Kolmogorov–Smirnov analysis; with p-values >0.05, the distribution was considered not different from normal.

Descriptive statistics were implemented with the following characteristics: arithmetic means (M), standard deviation, and percentage (%). In the case of normal

distribution, the Student's test was used to compare two independent samples, and in the case of other than the normal distribution, the Mann–Whitney and $\chi 2$ tests or Leven test were used with the definition of F. The Wilcoxon W-test was used to compare quantitative data within the group before and after treatment. Obtained differences were considered statistically significant at $p < 0.05$.

RESULTS

The study on HRV revealed significant differences between the analyzed groups. Thus, in group 1 (CHD + DM2) the average HR parameter was higher and CI was lower (Table 2). HRV disorders in group 1 (CHD + DM2) were evidenced by mean, SDNN, and pNN50 time parameters, which appeared to be lower than group 2 (CHD). APV parameters also differed between the groups.

Table 2. Comparative Analysis of Heart Rhythm and Arterial Pressure Variability in the Study Groups

Parameters	Group 1	Group 2	p
n	210	64	
Average heart rate, beat/min	88.24 ± 5.45	70.21 ± 3.18	***< 0.05***
SDNN, ms	108.6 ± 3.4	124.8 ± 4.3	***< 0.05***
RMSSD, ms	22.48 ± 3.16	28.7 ± 4.56	> 0.1
pNN50, %	6.31 ± 0.78	9.19 ± 0.92	***0.05***
Circadian index	1.16 ± 0.03	1.27 ± 0.04	***0.05***
Arterial pressure variability indexes, %			
-systolic, daytime	20.34 ± 1.81	15.34 ± 1.77	***< 0.05***
-diastolic, daytime	15.33 ± 0.88	12.46 ± 0.53	***< 0.05***
-systolic, nighttime	15.38 ± 1.52	11.80 ± 0.88	***< 0.05***
-diastolic, nighttime	12.63 ± 0.79	11.60 ± 0.85	> 0.1

The CCT result evaluation revealed no cases with the score of >4 in group 2 (CHD), i.e., the data in favor of CAN were absent, whereas the score of >4 was detected in 22% of patients in group 1 (CHD + DM2), which indicated the clinical stage of CAN; with this, in these patients, HRV and APV parameters went beyond the age-related norm. Consequently, the detected changes in HRV and APV parameters can be interpreted as CAN manifestations. Additionally, the number of patients with HRV and APV deviations in group 1 (CHD + DM2) was significantly higher (43%) than of those with impaired CCT scores (22%, $p < 0.05$). Thus, changes in HRV and APV with normal values of CCT scores may evidence the existence of the preclinical stage of CAN. Here, HRV disorders were more commonly identified in these patients (70%), and only 30% had HRV and APV disorders. Thus, the earliest manifestations of CAN in patients with a combination of CHD and DM2 may be HRV disorders, to which APV disorders add, and only later distinct clinical signs appear detecting CAN using CCT.

During the 6 months of treatment, the HbA1c level decreased from 8.38% ± 0.56% to 6.9% ± 0.26% in 1G group using iSGLT2 ($p < 0.05$), whereas from 8.28% ± 0.32% to 7.30% ± 0.29% in 2C group ($p < 0.05$). With this, achievement of the HbA1c target values in 1G group was coupled with bodyweight reduction, wherein the average BMI decreased from 33.62 ± 1.23 to 31.14 ± 1.06 kg/m^2, whereas a tendency of increased BMI from 32.76 ± 1.08 to 35.83 ± 1.1 kg/m^2 in 1C group, which finally began to exceed this parameter in 1G group. The frequency of hypoglycemic states was also different in the analyzed groups. In the 1G group, only 2 patients had signs of hypoglycemia, whereas 48% of patients noted hypoglycemia in the 1C group, with an increased dose of sulfonylurea preparations. All patients in the 1G group noted the quality of life improvement that was associated with increased exercise tolerance, decreasing shortness of breath, and stabilized arterial pressure. In the 1C group, only 3 patients noted the quality of life improvement (15%, $p < 0.05$).

The dynamics of HRV, APV, and CCT parameters were also different in 1G and 1C groups. Thus, in 1G group with iSGLT-2 treatment, the average HR per day decreased from 86.7 ± 2.4 beat/min to 76.7 ± 2.1 beat/min ($p < 0.05$), whereas CI increased from 1.19 ± 0.02 to 1.30 ± 0.01 ($p < 0.05$, Figure 1). Of attention is the dynamics of SDNN (an integrated parameter that characterizes HRV in general and depends on the influence of both sympathetic and parasympathetic divisions of the autonomic nervous system on the sinus node [14]), which increased from 106.1 to 114.034 ms ($p < 0.05$). This was mainly due to the influence of the parasympathetic division of the autonomic nervous system evidenced by an increase of the initially reduced RMSSD (from 19.83 ± 1.56 to

24.22 ± 1.51 ms, p < 0.05) and PNN50 (from 6.28 ± 0.88 to 10.04 ± 0.92, p < 0.05). Obtained results may indicate probable functional state improvement of the autonomic nervous system using iSGNT-2. This was also evidenced by the 24HAPM results: reduction of SAPd variability indices in 1G group (from 22.9 ± 1.7 to 16.4 ± 1.9%, p < 0.05), as well as SAPn (from 16.8 ± 2.2 to 12.3 ± 2.6%, p < 0.05, Figure 2).

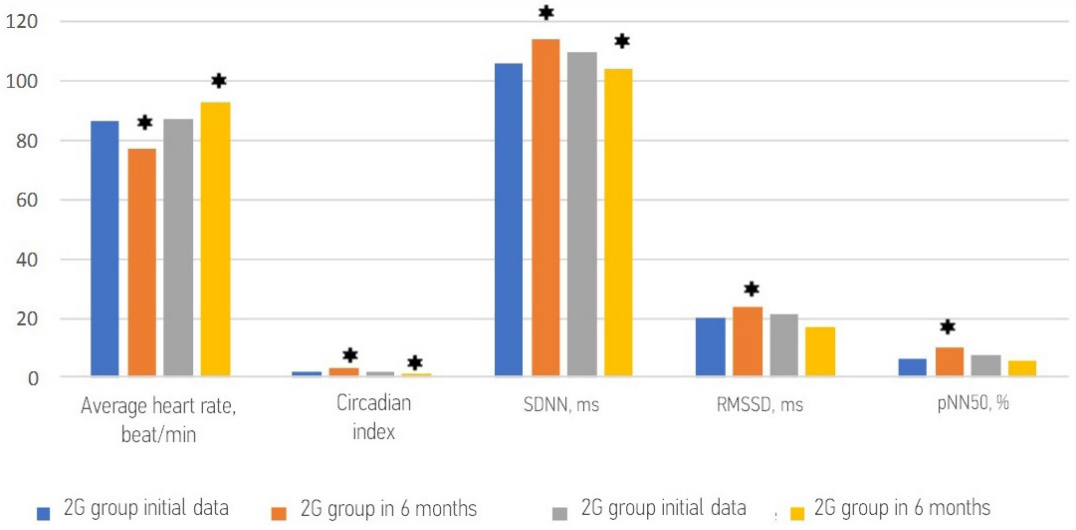

Fig. 1. Dynamics of parameters of heart rhythm variability in patients of 1G (receiving empagliflozin) and 1C (continuing the earlier selected treatment) groups in 6 months of treatment.
Note: * — differences with the corresponding initial parameter with p < 0.05.

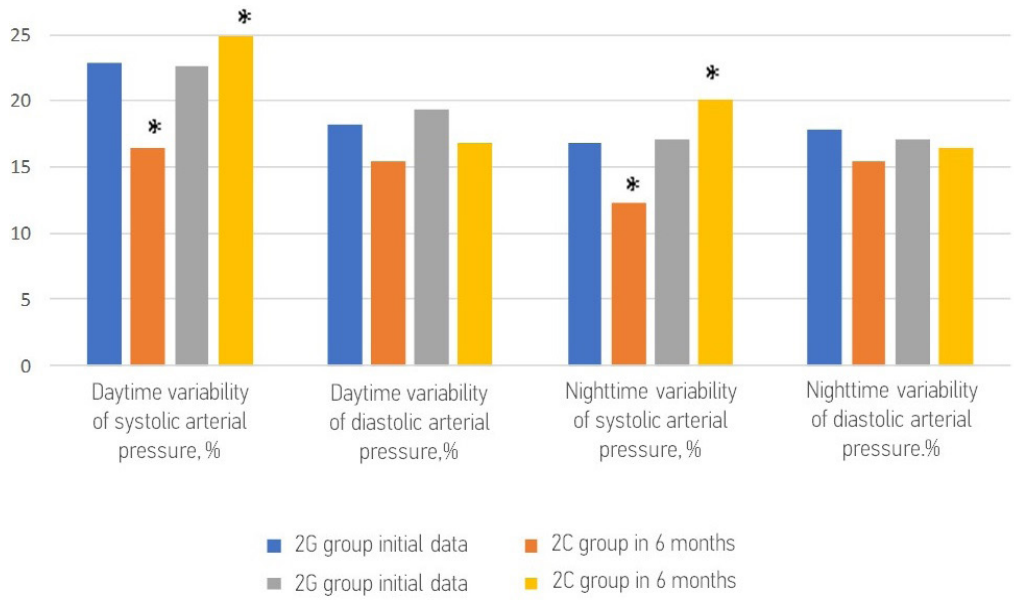

Fig. 2. Dynamics of parameters of arterial pressure variability in patients of 1G (receiving empagliflozin) and 1C (continuing the earlier selected treatment) groups in 6 months of treatment.
Note: * — differences with the corresponding initial parameter with p < 0.05.

In the 1C group, the 24HECGM and 24HAPM results were different. The average HR per day increased (from 86.7 ± 2.5 to 92.4 ± 1.9 beat/min, p < 0.05), whereas CI decreased (from 1.17 ± 0.04 to 1.08 ± 0.01, p < 0.05). Contrary to the 1G group, SDNN parameter decreased (from 110.20 ± 2.22 to 104.01 ± 2.1 ms, p < 0.05), and a tendency to reduced RMSSD and PNN50 (p > 0.05) was seen. Based on the results of 24HAPM, increased SAPd index (from 22.6 ± 1.3 to 24.9 ± 1.6%, p < 0.05) and SAPn index (from 17.1 ± 2.4 to 20.1 ± 1.6%, p < 0.05) was found in 1C group. In repeated CCT conducted in 6 months, the score in the 1G group did not show any

significant changes and remained at <4.0 in all patients, whereas it exceeded 4.0 in 26% of patients in the 1C group ($p < 0.05$), which may be indicative of CAN progression.

DISCUSSION

CCT does not always permit CAN identification, especially in the early stages. HRV investigation using the data of 24HECGM and APV using the data of 24HAPM can be suggested to provide a more objective judgment about the presence of CAN and verify this complication of DM2 at the preclinical stage.

The use of CCT identified CAN in the group with a combination of CHD and DM2 only in 22% of patients, while the real number of patients may be 43% based on HRV and APV parameter evaluation. Here, the first manifestations of the preclinical stage may be deviations of HRV parameters, and disorders in APV added with the progression of CAN.

The use of iSGLT-2 empagliflozin in the early stages of CAN reduced the clinical manifestations of CHD with the underlying HRV improvement due to the reduced average HR, increased CI, and improved time characteristics. Positive dynamics of APV concerned only systolic AP that was manifested in SAPd and SAPn indices improvement.

CONCLUSIONS

1. HRV and APV disorders based on the data of the 24HECGM and 24HAP were identified in 43% of patients with CHD in combination with DM2. Simultaneous assessment of the study parameters considerably optimized diagnosis of the preclinical stage of the cardiovascular form of diabetic autonomic neuropathy.

2. A positive dynamics of HRV and APV parameters was noted against the background treatment with empagliflozin, which demonstrated the capacity to improve the functional condition of the autonomic nervous system at the preclinical stage of the cardiovascular form of diabetic autonomic neuropathy.

3. Along with stabilized carbohydrate metabolism parameters, the use of empagliflozin led to reduced body weight with the minimal risk of hypoglycemic conditions in patients with comorbidities at high cardiovascular risk.

ADDITIONAL INFORMATION

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Contribution of the authors: *A. V. Kotskaya* — collection, translation and analysis of the material, concept and design of the study, writing the text; *E. V. Salaychuk* — statistical processing, writing the text; V. I. Kudinov — editing; *V. P. Terent'yev* — editing; *M. S. Lankina* — concept of the literary review. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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