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OPTIMIZATION OF VENTRICULAR ARRHYTHMIAS DIAGNOSTICS: ASSESSING THE DYNAMICS OF THE REGULATORY-ADAPTIVE STATUS

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Abstract. ***Introduction.*** Criteria for the effectiveness of therapy for ventricular arrhythmias (VA) take into account only the antiarrhythmic effect of pharmacological agents, which does not correspond to the modern personalized approach in medicine. Currently beta-blockers (BB) have the greatest evidence base in the treatment of VA. Their hypotensive and antianginal properties have been sufficiently studied. However, there is evidence of a possible negative impact of BB on the regulatory-adaptive status (RAS), characterizing the global functional state, ability to regulate and adapt. Thus, the issues of optimizing diagnostics in patients with VA are relevant. ***Aim.*** To study the effect of β-blockers on the parameters of the cardiorespiratory synchronism (CRS) test in patients with VA. ***Materials and methods.*** The study included 120 patients with VA and essential hypertension (EH) or its combination with coronary heart disease (CHD), randomized into three groups for the treatment of BB with different pharmacochemical properties: bisoprolol, nebivolol and sotalol. As part of combination therapy, an angiotensin-converting enzyme inhibitor, lisinopril, was prescribed, and if indicated, a disaggregant, acetylsalicylic acid, and a lipid-lowering drug, atorvastatin. Initially and after 24 weeks of therapy, the following were performed: CRS test, daily monitoring of the electrocardiogram and blood pressure. ***Results.*** In all three groups of patients, comparable hypotensive and antiarrhythmic effects were recorded. When nebivolol was prescribed as part of combination therapy in patients with VA against the background of stage III EH or its combination with CHD, an increase in the synchronization range and RAS index was observed, in contrast to bisoprolol and sotalol. ***Conclusion.*** In patients with VA and EH or its combination with CHD, the CRS test makes it possible to determine the optimal combination therapy option that has the most positive effect on the functional state and RAS index.

Key words: regulatory-adaptive status; ventricular arrhythmias; bisoprolol; nebivolol; sotalol.

ОПТИМИЗАЦИЯ ДИАГНОСТИКИ ЖЕЛУДОЧКОВЫХ НАРУШЕНИЙ РИТМА СЕРДЦА: ОЦЕНКА ДИНАМИКИ РЕГУЛЯТОРНО-АДАПТИВНОГО СТАТУСА

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Резюме. ***Введение.*** Критерии эффективности терапии желудочковых нарушений ритма сердца (ЖНРС), как правило, учитывают лишь антиаритмическое действие фармакопрепаратов, что не соответствует представлению о персонифицированном подходе в медицине. Наибольшей доказательной базой в лечении ЖНРС в настоящее время обладают бета-адреноблокаторы (БАБ). В достаточной степени изучены гипотензивные и антиангинальные их свойства, однако имеются данные о негативном влиянии БАБ на регуляторно-адаптивный статус (РАС), характеризующий глобальное функциональное состояние организма, его способность к регуляции и адаптации. В связи с этим вопросы оптимизации диагностики у пациентов с ЖНРС представляются актуальными. ***Цель.*** Изучить влияние БАБ на параметры пробы сердечно-дыхательного синхронизма (СДС) у пациентов с ЖНРС. ***Материалы и методы.*** В исследование включено 120 пациентов с ЖНРС и гипертонической болезнью (ГБ) или ее сочетанием с ишемической болезнью сердца (ИБС), рандомизированных в три группы для лечения БАБ с различными фармакохимическими свойствами: бисопрололом, небивололом и соталолом. В составе комбинированной терапии назначались ингибитор ангиотензин-превращающего фермента — лизиноприл, а при наличии показаний дезагрегант — ацетилсалициловая кислота и гиполипидемический препарат — аторвастатин. Исходно и через 24 недели терапии проводились: проба СДС, суточное мониторирование электрокардиограммы и артериального давления. ***Результаты.*** Во всех трех группах пациентов регистрировались сопоставимые гипотензивные и антиаритмические эффекты. При назначении небиволола в составе комбинированной терапии у пациентов с ЖНРС на фоне ГБ III стадии или ее сочетания с ИБС отмечалось увеличение диапазона синхронизации и индекса РАС, в отличие от бисопролола и соталола. ***Заключение.*** У пациентов с ЖНРС и ГБ или ее сочетания с ИБС проба СДС позволяет определить оптимальный вариант комбинированной терапии, наиболее позитивно влияющий на функциональное состояние и индекс РАС.

Ключевые слова: регуляторно-адаптивный статус; желудочковые нарушения ритма сердца; бисопролол; небиволол; соталол.

INTRODUCTION

In the context of a modern personalized approach in medicine interest in methods of investigation the body's functional state characterizing global health parameters — quality of life, tolerance to exercise, regulatory-adaptive status (RAS) is expected to increase. [1, 5].

RAS index, integral parameter of cardiorespiratory synchronism (CRS) test considering interaction of the two main vegetative functions — cardiac and respiratory, has been devised and is being introduced into clinical practice for evident based quantitative evaluation of RAS [13]. The test has been devised at the department of normal physiology of Kuban State Medical University under the head of the professor V.M.Pokrovskiy. To record CRS a portable automated system is used (Fig. 1) [6].

The baseline HR (BHR) and synchronization range (SR) parameters — the width of the range, minimal and maximal limits, duration of synchronization development at a minimal and maximal limits (DSD_{min}) are assessed during the test (Fig. 2). After that, on the basis of the data received RAS is calculated using the formula: RAS index = synchronization range width / duration of synchronism development at a maximal level × 100. RAS index of 100 and higher means high regulatory-adaptive reserve, 99–50 — good, 49–25 — satisfactory, 24–10 — low, 9 and lower — unsatisfactory [14].

Findings of clinical investigations of RAS index in healthy individuals and patients with different pathologies have been published in recent years. Differences of RAS index in a person according to the age and gender characteristics, personal peculiar features and temperament are determined. A clear reverse correlation of RAS index and severity of the pathological process have been demonstrated in patients of obstetric-gynecologic, surgical and therapeutic profiles, in clinics of neurology and psychiatry, sports and military medicine [4, 14].

At the same time, scientific literature has it that positive progress of aimed clinical parameters on treatment is not always accompanied by functional parameters improvement [1]. Thus, in patients with chronic heart failure (CHF) without marked sympathicotonia effective therapy with BB metoprolol succinate use led to no RAS improvement [2].

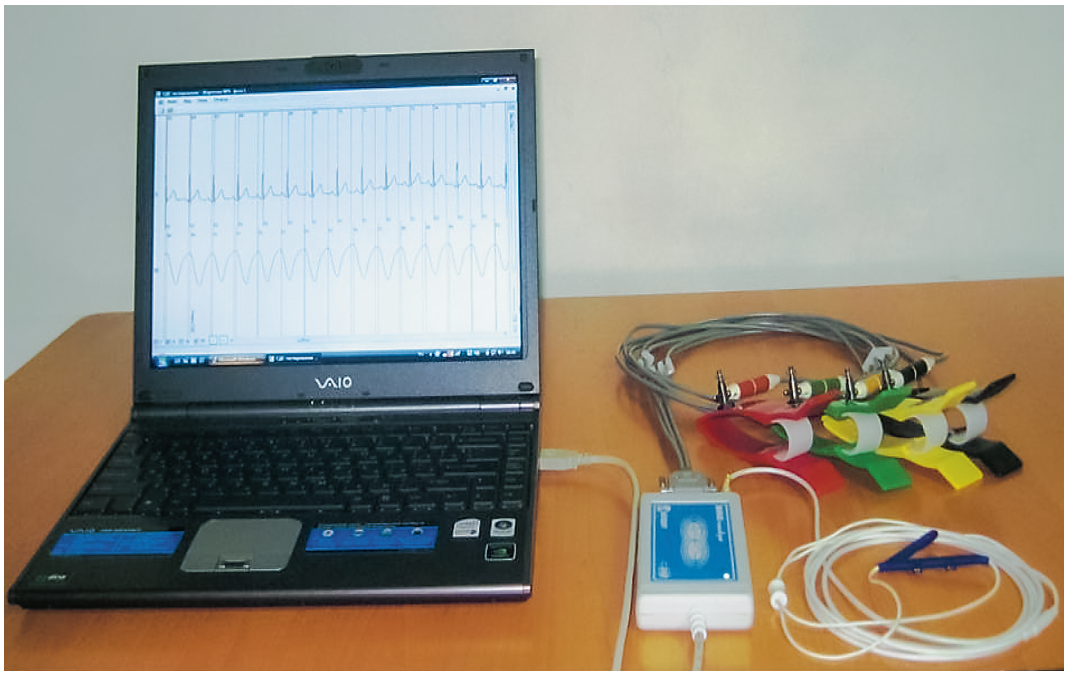

Fig. 1. Portable system for obtaining cardiorespiratory synchronism and analyzing its parameters in humans
Рис. 1. Портативная система для изучения сердечно-дыхательного синхронизма и анализа его параметров у человека

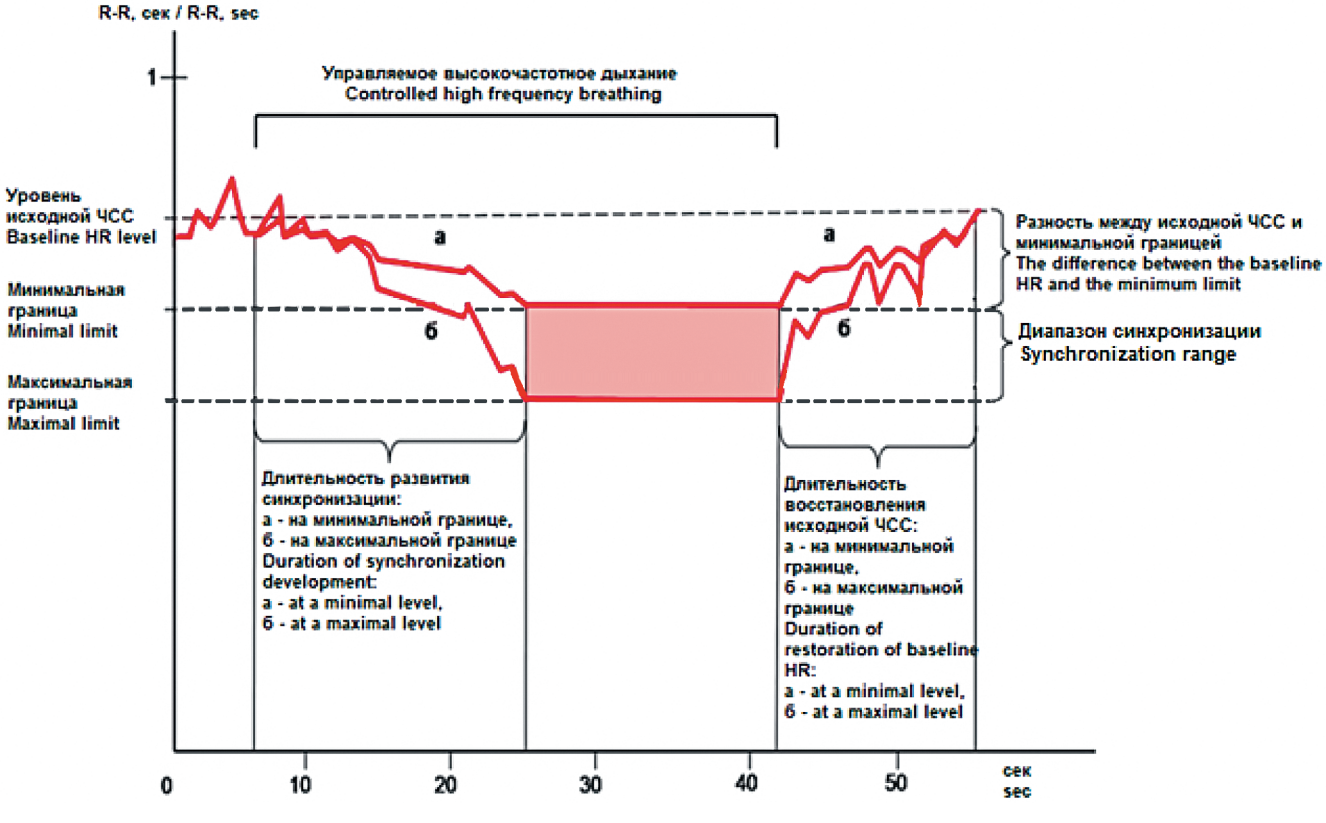

Fig. 2. Indicators of cardiorespiratory synchronism
Рис. 2. Пример показателей сердечно-дыхательного синхронизма

The mentioned phenomenon is likely to be due to specific pharmaceutical drug effect on the affected chains of the vegetative nervous system.

BB are widely used in the routine cardiological practice. Their prescription is most relevant in VA. Ventricular arrhythmias wide spreading and impact on both the prognosis and quality of life explain increased scientific and practical interest in this form of the heart rhythm disorder [8]. Despite the available literature information, currently there is no clearly stated VA treatment strategy. The leading criteria of pharmacotherapy effectiveness is traditionally thought to be the achievement of the antiarrhythmic effects targeted [15]. It is evident that the question of optimal medicine choice should not be reduced to curing arrhythmia. The antiarrhythmic drugs use should provide both achieving clinical effects targeted and positive effect on the functional body state as a whole.

In previous studies reproducibility of CRS and sufficient RAS index responsitivity in patients with VA were shown. And the impact of arrhythmic syndrome etiology and its severity on the RAS index have been demonstrated [7]. However, in modern literature there is no enough evident of BB with different pharmacochemical properties effect on RAS of patients with VA.

OBJECTIVE OF THE STUDY

To study the effect of β-blockers on the parameters of the CRS test in patients with VA.

MATERIALS AND METHODS

The study was carried out on the basis of department of normal physiology of Federal State Budget Educational Institution of Higher Education “Kuban State Medical University” of Ministry of Health of the Russian Federation, department of pathological physiology of Federal State Budget Educational Institution of Higher Education “Military Medical Academy named after S.M. Kirov” of Ministry of Defense of the Russian Federation and department of cardiology of the State Budget Healthcare Institution “Krai clinical hospital № 2” of Ministry of Health of Krasnodar Krai. The study was performed following ethics principles of Declarations of Helsinki [17] and with approval of independent Ethics Committee of FSBEI HE “Kuban State Medical University” of Ministry of Health of the Russian Federation (minute № 65 dated 21.09.2018).

The object of research was 120 people with VA with underlying stage III EH or its combination with coronary heart disease (CHD) who were later randomized into three groups with 40 patients in accordance with antiarrhythmic medicine prescribed as a part of combined therapy: group 1 — bisoprolol, group II — nebivolol and group III — sotalol.

Criteria for inclusion were: age 30–70 years, I–IV grades VA according to B.Lown classification, I–II — according to J.T. Bigger classification, symptomatic hemodynamically insignificant with stage III EH presence and its combination with CHD with safe left ventricle systolic function (ejection fraction ≥50%), without preceding 2 week treatment with prescribed drugs.

Exclusion criteria were: past acute cerebral and cardiac vascular accidents, effort-induced angina pectoris of high grades (III–IV functional classes), severe hypertension (III degree), CHF of high grades (III–IV functional classes) by New-York Heart Association classification and left ventricular systolic dysfunction, contraindications to the medicines being tested, past cardiosurgical and neurosurgical interventions, drug and alcohol abuse, decompensated respiratory, hepatic and renal failure, malignant neoplasms, autoimmune diseases in the exacerbation phase, decompensated endocrine diseases, pregnancy and lactation.

Initial daily dose of bisoprolol and nebivolol is 2.5 mg (a single intake), sotalol — 80 mg (in two divided doses). Daily doses varied with the interval of 14–28 days: bisoprolol and nebivolol — up to 10 mg, sotalol — up to 320 mg (hemodynamic and subjective ecceptability parameters were taken into account). All participants of the study were administered lisinopril, and if necessary atorvastatin in daily dose of 16.1±4.9 mg (n=17), 15.4±4.8 mg (n=15), 15.7±5.1 mg (n=19) and acetylsalicylic acid in daily dose of 94.2±17.7 mg (n=20), 92.8±17.1 mg (n=22), 93.2±15.6 mg (n=12) in the groups correspondingly (Table 1).

Initially and after 24 weeks of treatment a complete physical examination was performed (Table 2).

Statistical processing was made by means of applied program set STATISCICS (version 6.0) and included methods of variation statistics with calculation of arithmetical mean (M), arithmetical mean standard deviation (SD), the t-Student criterion after evaluating the sample according to the Kolmogorov-Smirnov criterion. The differences were considered statistically significant at $p < 0.05$.

RESULTS

In group I on combined therapy with bisoprolol there was a decrease of RAS (according to the CRS test duration of synchronism development at the minimal level of the synchronization range increased by 26.3% ($p < 0.01$), synchronization range decreased by 19.2% ($p < 0.01$) and RAS index decreased by 38.6% ($p < 0.01$)). At the same time antiarrhythmic effects targeted were induced (according to the daily electrocardiogram monitoring the average HR reduced by 21.1% ($p < 0.01$), the number of ventricular premature beats — by 77.3% ($p < 0.05$), number of episodes of ventricular allo-

Table 1

Baseline data of patients with VA included in the study and doses of the main pharmacological agents used (M±SD)

Таблица 1

Исходные данные включенных в исследование пациентов с ЖНРС и дозы основных применяемых фармакопрепаратов (M±SD)

Показатель / Indicator	Группа I / Group I (n=40)	Группа II / Group II (n=40)	Группа III / Group III (n=40)
Возраст (годы) / Ages (years)	53,2±10,8	52,1±12,7	49,8±11,2
Пол (мужчины / женщины) / Gender (men/women)	19 / 21	20 / 20	21 / 19
Длительность ГБ (годы) / Duration of EH (years)	7,1±2,3	6,8±2,0	6,7±2,1
Длительность ИБС (годы) / Duration CHD (years)	4,8±1,2	4,1±1,3	4,5±1,4
ЧСС (в 1 минуту) / HR (in 1 minute)	78,7±9,8	80,2±10,4	81,2±12,3
Артериальное давление: / Blood pressure: / – систолическое / systolic – диастолическое (мм рт.ст.) / diastolic (mm Hg)	 152,1±10,1 98,3±4,1	 158,9±12,2 97,0±4,8	 156,0±10,8 98,6±5,4
БАБ / beta blocker суточная доза (мг в сутки) / daily dose (mg per day)	Бисопролол / Bisoprolol 6,7±1,4	Небиволол / Nebivolol 6,4±2,8	Соталол / Sotalol 166,5±49,1
Лизиноприл / Lisinopril суточная доза (мг в сутки) / daily dose (mg per day)	12,0±4,6	13,5±4,1	14,7±4,5

Table 2

Research methods

Таблица 2

Методы исследования

Метод / Method	Аппарат / Apparatus	Цель исследования / Purpose of the study
Проба СДС [5] / CRS test	ВНС МИКРО (производитель Россия) / VNS MICRO (manufacturer Russia)	Количественная оценка регуляторно-адаптивного резерва / Quantitative assessment of the regulatory-adaptive reserve
Суточное мониторирование электрокардиограммы (СМЭКГ) [11] / Daily electrocardiogram monitoring	МИОКАРД ХОЛТЕР (производитель Россия) / MYOCARD HOLTER (manufacturer Russia)	Контроль антиаритмической эффективности лечения / Monitoring the antiarrhythmic effectiveness of treatment
Суточное мониторирование артериального давления (СМАД) [12] / Daily blood pressure monitoring	BPLab (производитель Россия) / BPLab (manufacturer Russia)	Контроль гипотензивной эффективности лечения / Monitoring the antihypertensive effectiveness of treatment

rhythmia — by 80.5% (p <0.05)). Moreover, according to the daily blood pressure monitoring targeted decrease of the average systolic arterial blood pressure in the day and night time by 21% (p <0.05) and 12,8% (p <0.05) correspondingly and average diastolic blood pressure in the day and night time by 17.9% (p <0.05) and 14% (p <0.05) correspondingly was observed.

In group II a combination of the combined treatment and nebivolol made it possible to improve RAS index (according to the CRS test SR increased by 34.8% (p <0.05), RAS index increased by 27.9% (p<0.05), duration of synchronism development at the minimal level of the synchronization range did not change essentially. At the same time antiarrhythmic effects targeted were induced (according to the daily electrocardiogram monitoring the average HR reduced by 16% (p <0.01), the number of ventricular premature beats — by 72.8% (p <0.05), number of episodes of ventricular allorhythmia — by 79.8% (p <0.05)). Apart from that, according to the daily blood pressure monitoring targeted decrease of the average systolic arterial blood pressure in the day and night time by 25.1% (p <0.05) and 18,2% (p <0.05) correspondingly and average diastolic blood pressure in the day and night time by 18.6% (p <0.01) and 17.1% (p <0.05) correspondingly was observed.

Table 3

Results of the CRS test in patients with VA after 24 weeks of therapy (M±SD)

Таблица 3

Результаты пробы СДС у пациентов с ЖНРС через 24 недели терапии (M±SD)

Показатель / Indicator	Группа I / Group I (n=40)	Группа II / Group II (n=40)	Группа III / Group III (n=40)
ДРСmin / Duration of synchronism development at the minimal level of the synchronization range	17,1±4,2 $p_{I–II}$<0,05 $p_{I–III}$<0,05	13,1±2,8 $p_{II–III}$>0,05	12,8±3,6
ДС / Synchronization range	5,9±1,7 $p_{I–II}$<0,05 $p_{I–III}$>0,05	10,2±2,5 $p_{II–III}$<0,05	6,8±2,0
Индекс РАС / RAS index	34,7±8,4 $p_{I–II}$<0,01 $p_{I–III}$<0,01	77,4±13,6 $p_{II–III}$<0,01	53,1±12,4

Примечание: $p_{I–II}$ — при сравнении показателя между группами I и II; $p_{I–III}$ — при сравнении показателя между группами I и III; $p_{II–III}$ — при сравнении показателя между группами II и III.
Note: $p_{I–II}$ — when comparing the indicator between groups I and II; $p_{I–III}$ — when comparing the indicator between groups I and III; $p_{II–III}$ — when comparing the indicator between groups II and III.

In group III the sotalol use in addition to the combined treatment was accompanied by RAS reduction (in accordance with CRS test there was a decrease of SR by 12.4% (p <0.01), RAS index by 13.7% (p <0.01), and there was no any significant change of duration of synchronism development at the minimal level of the SR). Thus, antiarrhythmic effects targeted were induced (according to the daily electrocardiogram monitoring the average HR reduced by 18.2% (p <0.01), the number of ventricular premature beats — by 77.1% (p <0.05), number of episodes of ventricular allorhythmia — by 80.6% (p <0.05)). Apart from that, according to the daily blood pressure monitoring targeted decrease of the average systolic arterial blood pressure in the day and night time by 24.3% (p <0.05) and 9,1% (p <0.05) correspondingly and average diastolic blood pressure in the day and night time by 19.9% (p <0.01) and 19.9% (p <0.05) correspondingly was observed.

The analysis of the finding progress differences between the groups showed that only in group II RAS status improvement was marked. At the same time, comparable antiarrhythmic and hypotensive effects were recorded in all the groups (Table 3).

DISCUSSION

In this study the comparison of three antiarrhythmic drugs with distinct pharmaco-chemical differences was performed. When studying clinical efficacy of bisoprolol, which belongs to the group of selective lipohydrophil antiarrhythmic medicines of class II, we paid attention to its ability to stabilize cellular membranes. In BIMS, BISOMET, TIBBS, MIRSA studies the efficacy was demonstrated in the prevention of myocardium remodeling in patients with chronic heart failure and a decrease of acute cardiac complications and total mortality in EH and CHD [3, 10].

No less effective lipophilic antiarrhythmic drug of class II is nebivolol with high cardiac selectiveness, which mediates vasodilatory effects due to nitrogen oxide (NO) synthesis by the endothelium. Unlike other BB it does not affect erectile function and also provides fat and carbohydrate metabolism improvement. In clinical projects MR NOED, NEBIS, SENIORS in treatment of EH, CHD and CHF nebivolol reduced total mortality and number of acute cardiac complications, caused left ventricular hypertrophy regressing and controlled arterial hypertension [16].

Sotalol is a hydrophilic nonselective BB presenting the properties of class III antiarrhythmic drugs, as well as the two previous drugs it demonstrated high clinical efficacy. In earlier clinical projects, such as ESVEM, VT-MASS, AVID, sotalol prevented supraventricular cardiac rhythm disorders and ventricular arrhythmias of high grades, provided arterial blood pressure improvement [9].

In this study bisoprolol, nebivolol and sotalol as part of combined therapy demonstrated comparable antiarrhythmic and hypotensive efficacy in patients with VA with underlying stage III EH or its combination with coronary heart disease (CHD), with differences of the drugs effect on the CRS test parameters being revealed. Nebivolol compared to bisoprolol and sotalol increased synchronization range and RAS index. Sotalol compared to bisoprolol increased duration of synchronism development at the minimal level of the synchronization range in a lesser degree, decreased RAS index less significantly.

Currently, there is no overwhelming scientific evidence explaining multidirectional effect of antiarrhythmic medicines on RAS revealed in the work. We suppose that diffe-

rences in the ability to penetrate through hematoencephalic barrier and different pharmacodynamic and pharmacokinetic properties of the mentioned drugs define the direction and degree of changes.

The results obtained require further detailed research within clinical and laboratory studies. The importance of global reserve, adaptive and regulatory reactions is ambiguously interpreted, the role of secondary organ and systemic pathological changes is overestimated. Thus, study of RAS helps estimate functional state of the organism, the impact of pathological process and pharmacotherapy on it that will allow us in future optimize and individualize program of treatment and prevention of cardio-vascular complications in patients of this category.

CONCLUSIONS

1. As part of combination therapy bisoprolol, nebivolol and sotalol caused equal targeted antiarrhythmic and hypotensive effects in patients with VA with underlying stage III EH or its combination with CHD.

2. While administering nebivolol as part of combination therapy patients with VA with underlying stage III EH and its combination with CHD were reported to have increased SR and RAS index compared to bisoprolol and sotalol.

3. The use of CRS test in patients with VA with underlying stage III EH and its combination with CHD makes it possible to determine the most suitable type of combined pharmacotherapy that does not affect RAS.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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Consent for publication. Written consent was obtained from the patients for publication of relevant medical information within the manuscript.

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Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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