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CONTENTS

ЗМІСТ

Fundamental researches	Фундаментальні дослідження	
<i>Khrypachenko I. A.</i> THE ROLE OF PARASYMPATHETIC AUTONOMIC REGULATION IN ENSURING OF RATS' RESISTANCE IN THE MODEL OF MULTIPLE ORGAN DYSFUNCTION	<i>Хрипаченко І. А.</i> РОЛЬ ПАРАСИМПАТИЧНОЇ ВЕГЕТАТИВНОЇ РЕГУЛЯЦІЇ У ЗАБЕЗПЕЧЕННІ СТІЙКОСТІ ЩУРІВ В МОДЕЛІ СИНДРОМУ ПОЛІОРГАННОЇ НЕДОСТАТНОСТІ	5
Clinical researches	Клінічні дослідження	
<i>Belal S. A. S., Vodyanitska N. A., Yabluchansky M. I.</i> THE INFLUENCE OF BIOFEEDBACK SESSIONS IN CLOSED LOOP OF HEART RATE VARIABILITY AND PACED BREATHING ON SYSTOLIC BLOOD PRESSURE CONTROL DURING STANDARD DRUG THERAPY IN PATIENTS WITH ARTERIAL HYPERTENSION	<i>Белал С. А. С., Водяницька Н. А., Яблучанський М. І.</i> ВПЛИВ СЕАНСІВ БІОЛОГІЧНОГО ЗВОРОТНОГО ЗВ'ЯЗКУ ІЗ ЗАМКНУТИМ КОНТУРОМ ВАРІАБЕЛЬНОСТІ СЕРЦЕВОГО РИТМУ І МЕТРОНОМІЗОВАНОГО ДИХАННЯ НА КОНТРОЛЬ СИСТОЛІЧНОГО АРТЕРІАЛЬНОГО ТИСКУ НА ТЛІ СТАНДАРТНОЇ МЕДИКАМЕНТОЗНОЇ ТЕРАПІЇ У ПАЦІЄНТІВ З АРТЕРІАЛЬНОЮ ГІПЕРТЕНЗІЄЮ	11
<i>Chernuskiy V. G., Govalenkova O. L., Letyago G. V.</i> A CONCOMITANT ANTIMICROBIAL ACTIVITY OF METHYLATED AND HALOGENATED GLUCOCORTICOSTEROIDS AGAINST MICROORGANISMS ISOLATED FROM THE SPUTUM OF CHILDREN WITH BRONCHIAL ASTHMA	<i>Чернуський В. Г., Говаленкова О. Л., Летяго Г. В.</i> СУПУТНЯ АНТИМІКРОБНА АКТИВНІСТЬ МЕТИЛ- І ГАЛОГЕНУТРИМУЮЧИХ ГЛЮКОКОРТИКОСТЕРОЇДІВ ПО ВІДНОШЕННЮ ДО МІКРООРГАНІЗМІВ, ВИДІЛЕНИХ З МОКРОТИННЯ У ДІТЕЙ, ХВОРИХ НА БРОНХІАЛЬНУ АСТМУ	22
<i>Dubyna S. O.</i> MORPHOMETRIC INDICATORS OF AN ORBIT AT ADULTS IN CONNECTION WITH TYPES OF CRANIUM	<i>Дубина С. О.</i> МОРФОМЕТРИЧНІ ПОКАЗНИКИ ОЧНОЇ ЯМКИ ДОРОСЛИХ ЛЮДЕЙ У ЗВ'ЯЗКУ З КРАНІОТИПАМИ	27
<i>Igorova A. Yu., Garkaviy P. O., Yabluchansky M. I.</i> OUTCOMES OF ARTERIAL HYPERTENSION IN PATIENTS WITH DIFFERENT TYPES OF SYSTOLIC BLOOD PRESSURE ORTHOSTATIC REACTIONS	<i>Єгорова А. Ю., Гарькавий П. О., Яблучанський М. І.</i> НАСЛІДКИ АРТЕРІАЛЬНОЇ ГІПЕРТЕНЗІЇ У ПАЦІЄНТІВ З РІЗНИМИ ТИПАМИ ОРТОСТАТИЧНИХ РЕАКЦІЙ СИСТОЛІЧНОГО АРТЕРІАЛЬНОГО ТИСКУ	35
<i>Maltseva M. S.</i> QTC INTERVAL DURATION CLASS AND STIMULATION PARAMETERS IN PATIENCE DURING FIRST SIX MONTHS AFTER PACEMAKER	<i>Мальцева М. С.</i> КЛАС ТРИВАЛОСТІ ІНТЕРВАЛУ QTC ТА ПАРАМЕТРИ СТИМУЛЯЦІЇ У ПАЦІЄНТІВ В ПЕРШІ ПІВРОКУ ПІСЛЯ ІМПЛАНТАЦІЇ ЕКС	39
<i>Martinyanova L. O.</i> GENERAL CARDIOVASCULAR RISK AND THE CLINICAL CONDITION OF PATIENTS WITH ATRIAL FIBRILLATION	<i>Мартим'янова Л. О.</i> ЗАГАЛЬНИЙ КАРДІОВАСКУЛЯРНИЙ РИЗИК ТА КЛІНІЧНИЙ СТАН ПАЦІЄНТІВ З ФІБРИЛЯЦІЄЮ ПЕРЕДСЕРДЬ	45
<i>Shanina I. V., Volkov D. E.</i> PACING PARAMETERS CHANGES IN PATIENTS WITH IMPLANTED PACEMAKER IN DIFFERENT QRS COMPLEX DURATION CLASSES AT THE ANNUAL OBSERVATION STAGE	<i>Шаніна І. В., Волков Д. Є.</i> ЗМІНИ ПАРАМЕТРІВ ЕЛЕКТРОКАРДІОСТИМУЛЯЦІЇ У ПАЦІЄНТІВ З ІМПЛАНТОВАНИМИ ЕКС В РІЗНИХ КЛАСАХ ТРИВАЛОСТІ QRS КОМПЛЕКСУ НА РІЧНОМУ ЕТАПІ СПОСТЕРЕЖЕННЯ	49

Clinical case	Клінічний випадок	
<p><i>Akhimienmhona P. D., Oreofe A. B., Belal S. A. S., Kulyk V. L.</i> EFFECTIVENESS OF BIOFEEDBACK IN A CLOSED LOOP OF HEART RATE VARIABILITY PARAMETERS AND PACED BREATHING IN PATIENTS WITH ARTERIAL HYPERTENSION IN REAL CLINICAL PRACTICE</p>	<p><i>Ахімемнона П. Д., Ореофе А. В., Белал С. А. С., Кулик В. Л.</i> ЕФЕКТИВНІСТЬ БІОЛОГІЧНОГО ЗВОРОТНОГО ЗВ'ЯЗКУ В КОНТУРІ ПАРАМЕТРІВ ВАРІАБЕЛЬНОСТІ СЕРЦЕВОГО РИТМУ І МЕТРОНОМІЗОВАНОГО ДИХАННЯ У ПАЦІЄНТІВ З АРТЕРІАЛЬНОЮ ГІПЕРТЕНЗІЄЮ В РЕАЛЬНІЙ КЛІНІЧНІЙ ПРАКТИЦІ</p>	53
<p><i>Tomina O. E., Kamenskaya E. P., Lebedynets P. V., Tomakh V. V.</i> POLYCYTHEMIA VERA AN EXAMPLE OF A CLINICAL CASE</p>	<p><i>Томіна О. Є., Каменська Є. П., Лебединець П. В., Томах В. В.</i> ІСТИННА ПОЛЦИТЕМІЯ НА ПРИКЛАДІ КЛІНІЧНОГО ВИПАДКУ</p>	59
<p><i>Tselik N. E., Shevchuk M. I.</i> TREATMENT OF ARTERIAL HYPERTENSION AND QTc INTERVAL DURATION THROUGH CLINICAL PRACTICE</p>	<p><i>Целік Н. Є., Шевчук М. І.</i> ТЕРАПІЯ АРТЕРІАЛЬНОЇ ГІПЕРТЕНЗІЇ І ТРИВАЛІСТЬ ІНТЕРВАЛУ QTc ЧЕРЕЗ КЛІНІЧНУ ПРАКТИКУ</p>	63
Review	Огляд	
<p><i>Petrenko O. V.</i> CHRONOTHERAPY OF HYPERTENSION: LITERATURE REVIEW</p>	<p><i>Петренко О. В.</i> ХРОНОТЕРАПІЯ ГІПЕРТОНІЧНОЇ ХВОРОБИ: ОГЛЯД ЛІТЕРАТУРИ</p>	71
Lecture	Лекція	
<p><i>Bogun L. V.</i> ANEMIA OF CHRONIC DISEASE</p>	<p><i>Богун Л. В.</i> АНЕМІЯ ХРОНІЧНИХ ЗАХВОРЮВАНЬ</p>	81

Fundamental researches

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**THE ROLE OF PARASYMPATHETIC AUTONOMIC REGULATION
IN ENSURING OF RATS' RESISTANCE IN THE MODEL OF
MULTIPLE ORGAN DYSFUNCTION SYNDROM**

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To assess contribution of autonomic regulation in multiple organ dysfunction syndrome (MODS) survival ensuring and to test hypothesis about possible correction of clinical course by modulating the activity of parasympathetic influences we performed experiments on rats' model of the MODS. It was determined that nonresistant animals differentiated by less intensity of parasympathetic regulation response. It was revealed that stimulation of cholinergic system decrease lethality in rats, and inhibits the power of high frequency regulatory effects on the heart rate.

KEY WORDS: multiple organ dysfunction syndrome model, heart rate variability, N-cholinoreceptors

**РОЛЬ ПАРАСИМПАТИЧНОЇ ВЕГЕТАТИВНОЇ РЕГУЛЯЦІЇ
У ЗАБЕЗПЕЧЕННІ СТІЙКОСТІ ЩУРІВ В МОДЕЛІ СИНДРОМУ
ПОЛІОРГАННОЇ НЕДОСТАТНОСТІ**

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Для оцінки вкладу вегетативної регуляції у забезпеченні виживаності при синдромі поліорганної недостатності та для перевірки гіпотези щодо можливої корекції клінічного перебігу шляхом модулювання активності парасимпатичних впливів, виконані експерименти на щурах в умовах моделі поліорганної недостатності. Встановлено, що нестійкі тварини відрізняються меншою реакцією з боку парасимпатичної регуляції. Показано, що стимуляція холінергічної системи знижує летальність щурів, та призводить до пригнічення потужності високочастотних регуляторних впливів на серцевий ритм.

КЛЮЧОВІ СЛОВА: модель синдрому поліорганної недостатності, варіабельність серцевого ритму, Н-холінорецептори

**РОЛЬ ПАРАСИМПАТИЧЕСКОЙ ВЕГЕТАТИВНОЙ РЕГУЛЯЦИИ
В ОБЕСПЕЧЕНИИ УСТОЙЧИВОСТИ КРЫС В МОДЕЛИ СИНДРОМА
ПОЛИОРГАННОЙ НЕДОСТАТОЧНОСТИ**

Хрипаченко И. А.

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Для оценки вклада вегетативной регуляции в обеспечение выживаемости при синдроме полиорганной недостаточности и для проверки гипотезы о возможности коррекции клинического течения путем модулирования активности парасимпатических влияний, выполнены эксперименты на крысах в условиях модели полиорганной недостаточности. Установлено, что неустойчивые животные отличаются меньшей реакцией со стороны парасимпатической регуляции. Показано, что стимуляция холинергической системы снижает летальность крыс, и приводит к угнетению мощности высокочастотных регуляторных влияний на сердечный ритм.

КЛЮЧЕВЫЕ СЛОВА: модель синдрома полиорганной недостаточности, вариабельность сердечного ритма, Н-холинорецепторы

INTRODUCTION

Multiple organ dysfunction syndrome (MODS) frequently described as consequences of systemic inflammatory response (SIR) may develop in the most different diseases, which characterized by relatively high lethality [1]. The most different links take participation in its formation, including autonomic nervous system, which role remaining not studied enough [2]. Previously findings about influence of autonomic regulation on rats' survival in the model of multiple organ dysfunction syndrome, made us to investigate the possibility of systemic inflammatory response correction by modulation of autonomic circuits of regulation activity.

Considering recently appeared in the papers data about possible involvement of N-cholinoreceptors in regulation of functional activity of lymphocytes, macrophages and other cells participating in inflammation we suppose that the parasympathetic activation may decrease the systemic inflammation and so decrease the lethality of rats in the experimental model of multiple organ dysfunction syndrome.

OBJECTIVE

The aim of the present study was assessment of the parasympathetic autonomic regulation role in survival of rats in MODS model.

MATERIALS AND METHODS

Experiments were performed on the 78 Wistar lab male rats with 220-250 g body weight, which kept in the standard vivarium conditions. Multiple organ dysfunction syndrome was simulated by cecal ligation and puncture (CLP) procedure [3]. It was performed under combined anesthesia with ether inhalation and intraperitoneal injection of sodium thiopental (75 mg/kg).

The autonomic regulation was assessed by heart rate variability (HRV) spectral analysis with the using of the computer-based cardiograph «Cardio Lab» (KhAI-Medica, Ukraine) with signal discretization frequency of 500 Hz. Spectral power of parasympathetic influence (HF) was calculated in the range from 0.6 to 3.0 Hz and compared with power of sympathetic influence (LF) in the range from 0.08 to 0.6 Hz.

In the 1st group of animals (34 rats) we assess survival rate and association of survival with individual changes of autonomic regulation in response to single-dose intramuscular injection of phenylephrine (2 mg/kg) and in response to development of MODS after two hours of animal's induction to the model.

In the 2nd group of animals (44 rats) we assess survival rate in condition of N-cholinoreceptors stimulation. For this purpose, animals expose to intravenously injections of acetylcholinesterase inhibitor – neostigmine (0.5 mg/kg) and M-cholinergic antagonist - atropine (1 mg/kg). Such injections we performed by caudal vein access at 30 min before CLP and every 2 hours after induction to MODS model. Total duration of pharmacological exposure was 8 hours.

All statistical calculations were performed using Statistica 6.0 (Stat Soft Inc., USA). Spectral characteristics in tables and text are presented as median (Me), minimal (Min) and maximal values (Max), lower (Qi) and upper (Q_n) quartiles. Significance of differences between spectral characteristics was assessed by Mann-Whitney test.

RESULTS AND DISCUSSION

As it was expected, in spite of strictly standardized conditions of experiment, rats were characterized by different resistance to the induction of the experimental model of MODS. On the basis of findings about animals survival rate in the 1st group we subdivided animals into group of highly resistant rats (survived during 10 days - 3 animals) and low resistant rats (died within 3 days - 32 animals).

The power spectral indexes changes in response to pharmacologic sympathetic stimulation in the subgroups of high- and low resistant rats are presented below (table).

In the subgroup of highly resistant animals adrenoreceptors stimulation by phenylephrine lead to increase of the autonomic regulative influences power. In the selected by us range of the low frequencies (LF) the value of spectral power is increasing in 5-fold and of the high frequencies (HF-range) this value is increasing in 4.4 fold. As a result, in highly resistant rats, pharmacologic adrenoreceptors stimulation did not change significantly the values of sympathovagal balance - relation of spectral powers in the low and high frequencies range.

Table

Power spectral indexes of rats' HRV before and after stimulation of α -adrenoreceptors

Power spectral indexes		highly resistant rats (n=3)		low resistant rats (n=31)	
		before	after	before	after
LF, ms ²	Me	0.11	0.54*	0.10	0.50*
	Min- Max	0.01-0.53	0.09 - 2.02	0.01 - 0.50	0.03 - 2.13
	Q _i - Q _u	0.06-0.20	0.32 - 1.24	0.07 - 0.19	0.41 - 1.17
HF, ms ²	Me	1.35	5.92*	1.54	4.50*
	Min- Max	0.32 - 3.23	0.28 - 7.83	0.46 - 4.50	0.43 - 6.95
	Q _i - Q _u	0.99 - 1.89	3.47 - 6.35	1.01 - 2.09	3.82 - 4.93

Note: * - intragroup differences are significant at $p < 0.05$.

In the subgroup of low resistant animals, the response of sympathetic regulation to stimulation of α -adrenoreceptors corresponds with so in rats of compared subgroup - the power of influences in the low frequency range made increase in 5-fold. However, the HF spectral power of HRV in the succumbed rats in response to injection of phenylephrine made increase only in 2.9-fold. At the same time as in the group of survived rats the value of sympathovagal balance is not changed after phenylephrine injection – 0.10 (0.01-0.33) before phenylephrine and 0.11 (0.01-0.60) after pharmacologic stimulation.

The group of low resistant rats demonstrated 2-fold increase in the power of sympathetic influences as compared with initial values - up to 0.20 ms² (0.11-0.42), after 2 hours of CLP ($p < 0.05$). Nevertheless, the value of spectral power in the range of high frequencies, reflective mainly of parasympathetic influences, had tendency to decrease – 1.12 ms² (0.50-2.73). As a result the sympathovagal balance in this subgroup has mount to 0.28 (0.10-2.73), which was significantly more than initial values ($p < 0.05$).

Thus, analysis of survival demonstrated that resistance of rats in the model of MODS was related to properties of their autonomic response. Highly resistant animals characterizes by more pronounced response of parasympathetic regulation to pharmacologic stimulation as compared with low resistant rats.

In response to CLP (development of an acute bacterial inflammation in the abdominal cavity and organ dysfunction), the highly resistant rats respond with balanced increase of HRV spectral power in both investigated

ranges, sympathetic and parasympathetic links of autonomic regulation.

Subgroup of low resistant animals in response to the MODS model characterized by less pronounced activation of sympathetic influences in the absence thereof significant changes in the tone of parasympathetic link of regulation. In the total, we find marked shift of sympathovagal balance toward domination of sympathetic influences in the low resistant animals.

The results of experiment in the 1st group of rats confirm presumption about possible suppression of systemic inflammatory response through N-cholinergic anti-inflammatory pathway during parasympathetic activation [4]. These results was the basis to perform experiments on the animals of 2nd group with purpose to investigate the possibility of increasing resistance of rats in the MODS model by modulating the activity of different links of autonomic regulation.

Despite of the long-continued cholinergic stimulation of 2nd group rats by combination of neostigmine and atropine injections the index of 3-day lethality in the MODS model didn't differ significantly from 1st group of rats – 93.2 % и 91.2 %, accordingly ($p = 0.371$). At the same time, the comparative analysis of time curves of rat's deaths in these groups demonstrates following features (fig. 1).

Under cholinergic stimulation, there were no any deaths during the first 15 hours after induction rats to the model. In the compared group almost 12 % of animals died. On the background of the neostigmine almost 32 % of rats survived 34 hours, whereas until this term in the compared group died 88.2 % of animals ($p < 0.001$).

The results are the evidence of long-continued pharmacological stimulation of the cholinergic system affects status and character of response of different parts of autonomic nervous system. All spectral indices of HRV in rats of this experimental group were lower than in other one. Intensity of these effects not equal

for sympathetic and parasympathetic parts of regulation Thus, after 2 hours of induction of animals to the MODS model the indices of spectral power of HRV in the range of low frequencies (sympathetic influences) were about equal in rats of 1st and 2nd experimental groups.

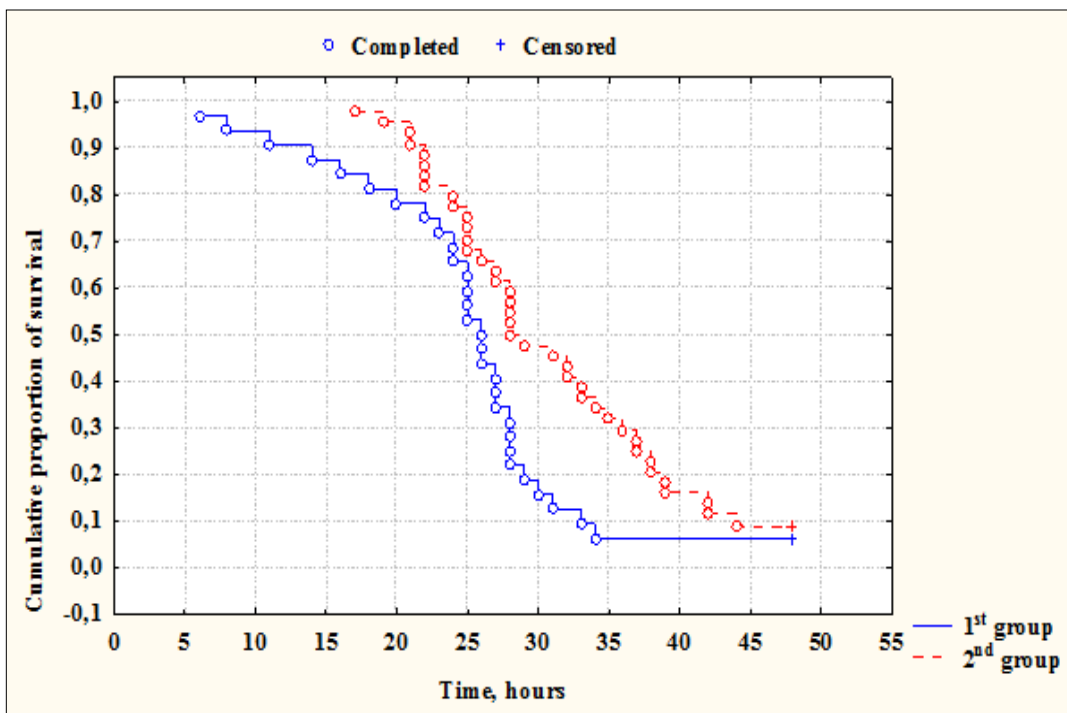


Fig. 1 Kaplan-Meier cumulative proportion of survival in rats' MODS model without (1st group, n=34) and with pharmacologic stimulation of cholinergic system (2nd group, n=44)

Neostigmine has more pronounced effects on the power of high frequencies of heart rhythm regulations (fig. 2). Mean values of spectral power index in rats with pharmacological stimulation of cholinergic nervous system were significantly ($p < 0.01$) lower ($4.72 \pm 1.61 \text{ ms}^2$), then in rats of compared group of investigation ($5.89 \pm 1.77 \text{ ms}^2$).

Our findings about ability of acetylcholinesterase inhibitor to decrease intra-experimental lethality of rats in MODS model is matched with results of other investigators, which were gained in other diseases models. Thus, it is known that stimulation of cholinergic receptors increases survival of rats after intraperitoneal injection of bacteria [4]. Experiments on the guinea pigs proved the ability of N-cholinoblockers to intensify of anaphylactic shock and, conversely, inhibition of

acetylcholinesterase prevent from development of shock [5].

With no relation to intensity and direction of effects of stimulation of the parasympathetic regulation demonstrated in different studies it is noteworthy that unity of settled opinion about the cause-and-effect relations between factors of systemic and local inflammation on the one hand and the status of different parts of the autonomic nervous system on the other.

Applied scheme of long-continued selective pharmacologic stimulation of N-cholinoreceptors, in our experiments, leads to significant inhibition of the power of high frequency regulatory influences on the heart rate. The same direction but less pronounced influences on the index of the spectral power of regulation in low frequency range (that reflect as is well known sympathotonic influences) was registered by us.

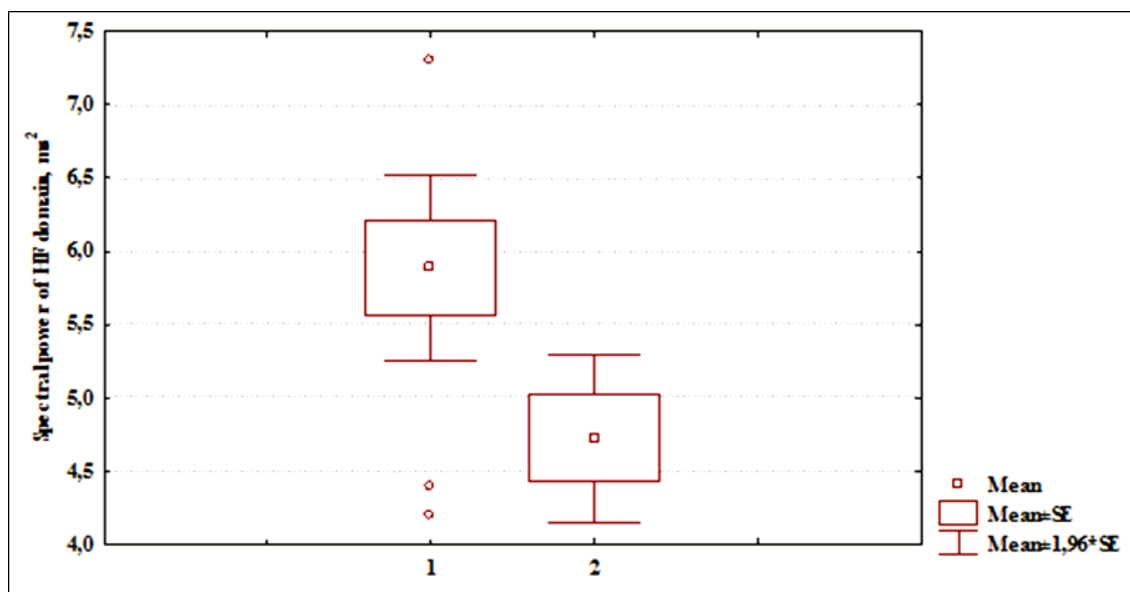


Fig. 2. HF spectral power of HRV in rats after 2 hours of induction to MODS model, without (1) and under (2) pharmacological stimulation of cholinergic system.

Our findings allow us to suggest that revealed influence of the cholinergic stimulation on the animals' survival in the experimental MODS realizes through the cytokine system. Thus, it is well known ability of cytokines to cause not only local but also distant effects on almost all organs and systems including tissues of central nervous system. This respectively would accompany with alterations in intensity and character of reflective responses, hormone and other biologic regulators synthesis [6]. On the other hand, electrical stimulation of vagal nerve inhibits synthesis of tumor necrosis factor in mice [4].

It must be underlined that revealed relations of the autonomic regulation status with factors of inflammation, is not specific for multiple organ dysfunction syndrome. Similar on direction but different in intensity patterns was described in studies of toxic injuries [7], in oncology clinics [8], in diabetes [9], and others.

CONCLUSIONS

Thus, our findings clarify understanding about the role of neurohumoral regulation in resistance of the body to the experimental model of multiple organ dysfunction syndrome.

Long-continued pharmacologic stimulation of N-cholinoreceptors decrease lethality in rats' model of multiple organ dysfunction syndrome, and significantly inhibits the power of high frequency regulatory influences on the heart rate.

PROSPECTS FOR FUTURE STUDIES

Our findings are justifying the reasonability of clinical approbation of medications, which effect on the autonomic nervous system and stimulate of its cholinergic link in patients with multiple organ dysfunction syndrome.

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Clinical researches

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THE INFLUENCE OF BIOFEEDBACK SESSIONS IN CLOSED LOOP OF HEART RATE VARIABILITY AND PACED BREATHING ON SYSTOLIC BLOOD PRESSURE CONTROL DURING STANDARD DRUG THERAPY IN PATIENTS WITH ARTERIAL HYPERTENSION

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Changes of systolic blood pressure (SBP) in biofeedback (BFB) sessions with closed loop of paced breathing (PB) and heart rate variability (HRV) during standard drug therapy of arterial hypertension (AH) was studied. 275 patients with 1-3 degree of AH (143 men and 132 women, mean age $58,55 \pm 7,99$ years) was divided into two comparable groups: 1 - BFB (139 patients) in investigated PB loop, 2 - control group (136 patients) with BFB without PB. In both groups was performed 10 sessions of BFB. Changes of SBP depending on the stage and degree of AH, gender and age was assessed. BP was measured by the method of Korotkov's with monometer Microlife BP AG1-20 in same conditions. Data were processed by parametric and nonparametric statistics. It is proved that the use of biofeedback in the loop of PB and HRV significantly ($p < 0.01$) exceeds in efficiency an isolated drug therapy in control of SBP at any stage and degree of AH in patients of both sexes in all age groups. Extent of the effect increases with the stage and degree of the disease and not related to the sex and age of the patient. Findings allow to recommend this technique in clinical practice.

KEY WORDS: arterial hypertension, biofeedback, heart rate variability, paced breathing, systolic blood pressure

ВПЛИВ СЕАНСІВ БІОЛОГІЧНОГО ЗВОРОТНОГО ЗВ'ЯЗКУ ІЗ ЗАМКНУТИМ КОНТУРОМ ВАРІАБЕЛЬНОСТІ СЕРЦЕВОГО РИТМУ І МЕТРОНОМІЗОВАНОГО ДИХАННЯ НА КОНТРОЛЬ СИСТОЛІЧНОГО АРТЕРІАЛЬНОГО ТИСКУ НА ТЛІ СТАНДАРТНОЇ МЕДИКАМЕНТОЗНОЇ ТЕРАПІЇ У ПАЦІЄНТІВ З АРТЕРІАЛЬНОЮ ГІПЕРТЕНЗІЄЮ

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Вивчено зміни систолічного артеріального тиску (САТ) в сеансах біологічного зворотного зв'язку (БЗЗ) із замкнутим контуром метрономізованого дихання (МД) і варіабельності серцевого ритму (ВСР) на етапах стандартної медикаментозної терапії артеріальної гіпертензії (АГ). 275 пацієнтів з 1-3 ступенем АГ (143 чоловіки та 132 жінки, середній вік $58,55 \pm 7,99$ років) розділені на дві зіставні групи: 1 - БЗЗ (139 пацієнтів) у вивченому контурі МД і 2 - група порівняння (136 пацієнтів) з БЗЗ без МД. В обох групах виконано по 10 сеансів БЗЗ. Оцінювали зміни САТ залежно від стадії та ступеня АГ, статі та віку пацієнтів. АД вимірювалося за методом Короткова монометром Microlife BP AG1-20 в однакових умовах. Дані оброблялися методами параметричної та непараметричної статистики. Доведено, що використання БЗЗ в контурі МД та ВСР достовірно ($p < 0,01$) перевершує по ефективності ізольовану медикаментозну терапію в контролі САД при будь-яких стадіях і ступенях АГ у пацієнтів обох статей у всіх вікових групах. Ступінь вираженості ефекту зростає зі збільшенням стадії і ступеня захворювання і не пов'язана зі статтю і віком пацієнта. Отримані дані дозволяють рекомендувати методику в клінічну практику.

КЛЮЧОВІ СЛОВА: артеріальна гіпертензія, біологічний зворотний зв'язок, варіабельність серцевого ритму, метрономізоване дихання, систолічний артеріальний тиск

ВЛИЯНИЕ СЕАНСОВ БИОЛОГИЧЕСКОЙ ОБРАТНОЙ СВЯЗИ С ЗАМКНУТЫМ КОНТУРОМ ВАРИАБЕЛЬНОСТИ СЕРДЕЧНОГО РИТМА И МЕТРОНОМИЗИРОВАННОГО ДЫХАНИЯ НА КОНТРОЛЬ СИСТОЛИЧЕСКОГО АРТЕРИАЛЬНОГО ДАВЛЕНИЯ НА ФОНЕ СТАНДАРТНОЙ МЕДИКАМЕНТОЗНОЙ ТЕРАПИИ У ПАЦИЕНТОВ С АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ

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Изучены изменения систолического артериального давления (САД) в сеансах биологической обратной связи (БОС) с замкнутым контуром метрономизированного дыхания (МД) и вариабельности сердечного ритма (ВСР) на этапах стандартной медикаментозной терапии артериальной гипертензии (АГ). 275 пациентов с 1-3 степенью АГ (143 мужчины и 132 женщины, средний возраст $58,55 \pm 7,99$ лет) разделены на две сопоставимые группы: 1 — БОС (139 пациентов) в изученном контуре МД и 2 — группа сравнения (136 пациентов) с БОС без МД. В обеих группах выполнено по 10 сеансов БОС. Оценивали изменчивость САД в зависимости от стадии и степени АГ, пола и возраста пациентов. АД измерялось по методу Короткова монOMETром Microlife BP AG1-20 в одинаковых условиях. Данные обрабатывались методами параметрической и непараметрической статистики. Доказано, что использование БОС в контуре МД и ВСР достоверно ($p < 0,01$) превосходит по эффективности изолированную медикаментозную терапию в контроле САД при любой стадии и степени АГ у пациентов обоих полов во всех возрастных группах. Степень выраженности эффекта возрастает с увеличением стадии и степени заболевания и не связана с полом и возрастом пациента. Полученные данные позволяют рекомендовать методику в клиническую практику.

КЛЮЧЕВЫЕ СЛОВА: артериальная гипертензия, биологическая обратная связь, вариабельность сердечного ритма, метрономизированное дыхание, систолическое артериальное давление

INTRODUCTION

Arterial hypertension (AH) is the most common chronic disease of the cardiovascular system in the adult population [1]. The greatest difficulty is the control of systolic blood pressure (SBP), which plays the leading role in the development of cardiovascular complications and significantly increases mortality [2].

One of the promising methods to increase the manageability of SBP can become biofeedback (BFB) in the closed loop of heart rate variability (HRV) and paced breathing (PB) [3].

Absence of data about the effectiveness of BFB in the loop of HRV and PB in the control of SBP in patients with arterial hypertension prompted us to perform this study.

The study was performed as part of research V. N. Karazin KhNU «Development and research of automatic system in heart rate variability control», № registration 0109U000622.

OBJECTIVE

The purpose of the study is to evaluate the changes of SBP in BFB sessions with the loop of HRV and PB in patients with AH.

MATERIALS AND METHODS

275 patients with AH (143 men and 132 women, mean age $58,55 \pm 7,99$ years) were observed. Inclusion criteria were systolic and systolic-diastolic AH in any stage and degree with the absence of systematic reception of any vasoactive medications in the past three months. Patients were excluded from the study in the case of isolated diastolic AH, acute myocardial infarction, unstable angina, stable angina with IV functional class, III stage of chronic heart failure, complex disorders of rhythm and conduction, comorbidities in others organs and systems.

In all patients blood pressure was measured by the Korotkov's method with monometer Microlife BP AG1-20 in the morning in a quiet, bright room in the sitting position after 15-minute rest. The accuracy of BP measurement is 0.5 mm Hg.

All patients were randomly assigned to two clinically comparable groups (table.): BFB group (139 patients) with the loop of PB and control group (136 patients) with BFB without MD.

Table

Clinical characteristics of patients with AH of comparable groups

Indices		Group	
		Biofeedback (139)	Comparison (136)
Sex, (n)	males	70	73
	females	69	63
Age	mean, (M \pm s d)	58,23 \pm 8,31	58,86 \pm 7,67
	mature, (n, M \pm sd)	66 (51,8 \pm 4,87)	68 (53,6 \pm 3,56)
	elderly, (n, M \pm sd)	65 (62,5 \pm 4,69)	59 (61,85 \pm 3,69)
	old, (n, M \pm sd)	8 (76,5 \pm 1,85)	9 (79,4 \pm 2,01)
AH stage, (n)	I	2	4
	II	115	110
	III	22	22
AH severity grade, (n)	Mild	14	15
	Moderate	51	62
	Severe	74	59
IHD	without	91	97
	SA	33	24
	PC	22	22
SA FC	without	106	113
	I	11	4
	II	10	9
	III	12	10
CHF stage	without	10	19
	I	59	55
	2A	57	55
	2B	13	7
CHF FC	without	10	19
	I	68	57
	II	43	42
	III	18	18

Note: IHD – ischemic heart disease; SAP - stable angina; PC - postinfarction cardiosclerosis; CHF – chronic heart failure; FC – functional class; without – patients without this indices.

BFB sessions were conducted on computer diagnostic complex «CardioLab 2009» («HAI-Medika») with built-in module «Biofeedback», which is the program-related audio-visual breathing metronome and algorithm for dynamically determining the current values of HRV parameters [4]. In both groups were performed 10 BFB sessions.

All patients were treated by the same therapy with antiplatelets, anticoagulants, beta-blockers, angiotensin converting enzyme inhibitors, calcium channel blockers, sartans, aldosterone antagonists, diuretics and statins in accordance with the recommendations for the prevention and treatment of AH from Ukrainian and European Societies of Cardiology [1, 5].

Groups of BFB and comparison were classified into subgroups depending on the stage and degree of AH, gender (women, men)

and age (adult, elderly, old in classification [6]) of the patients.

In the groups and subgroups of patients the mean (M) and standard deviation (sd) of the SBP was evaluated after entering data into the Microsoft Excel table. The significance of differences between values of SBP in groups and subgroups at stages of the study was determined by using the U-Mann-Whitney-test [7] and inside groups at current stages against the values before the treatment - by using T-Wilcoxon test [8].

RESULTS AND DISCUSSION

Changes of SBP mean values in groups of BFB and comparison in stages of the study are shown in Fig. 1. At the same medication in groups systematic BFB sessions has contributed to significantly ($p < 0.01$) lower values of SBP in 9 day of the treatment.

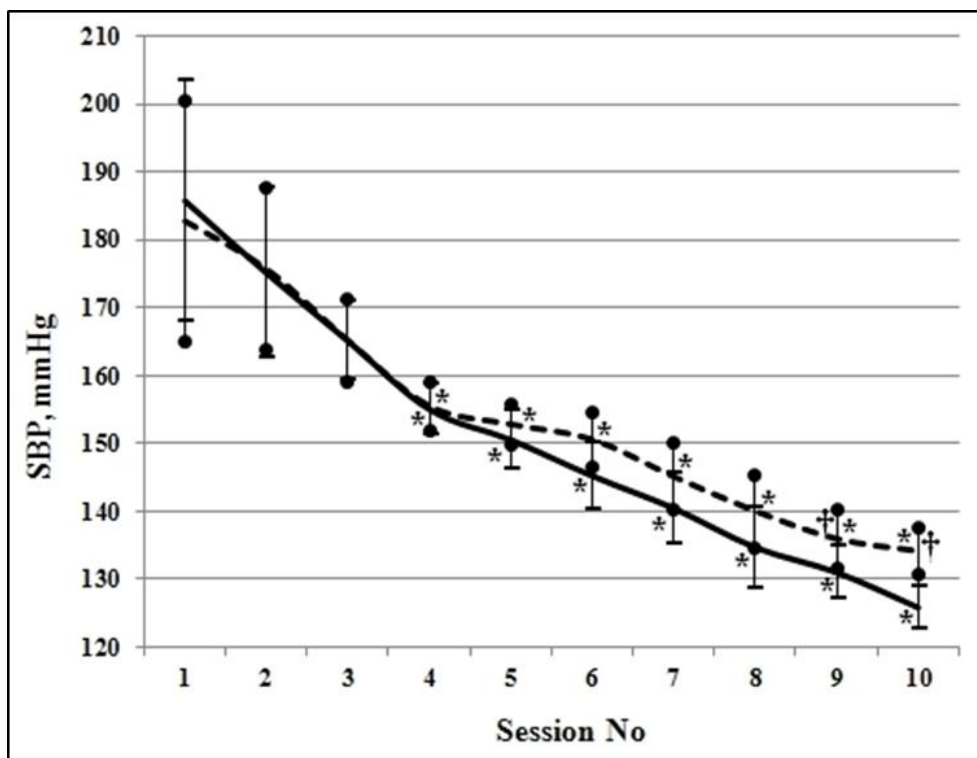
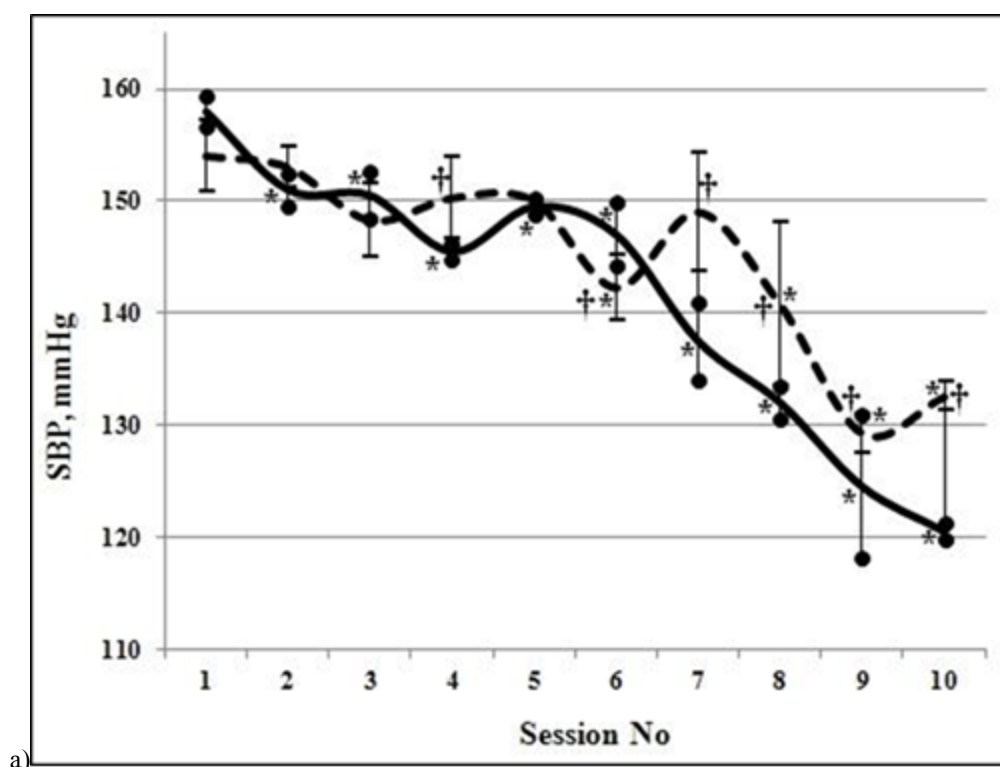


Fig. 1. Changes of SBP mean values for all patients in groups of BFB and comparison at stages of observation

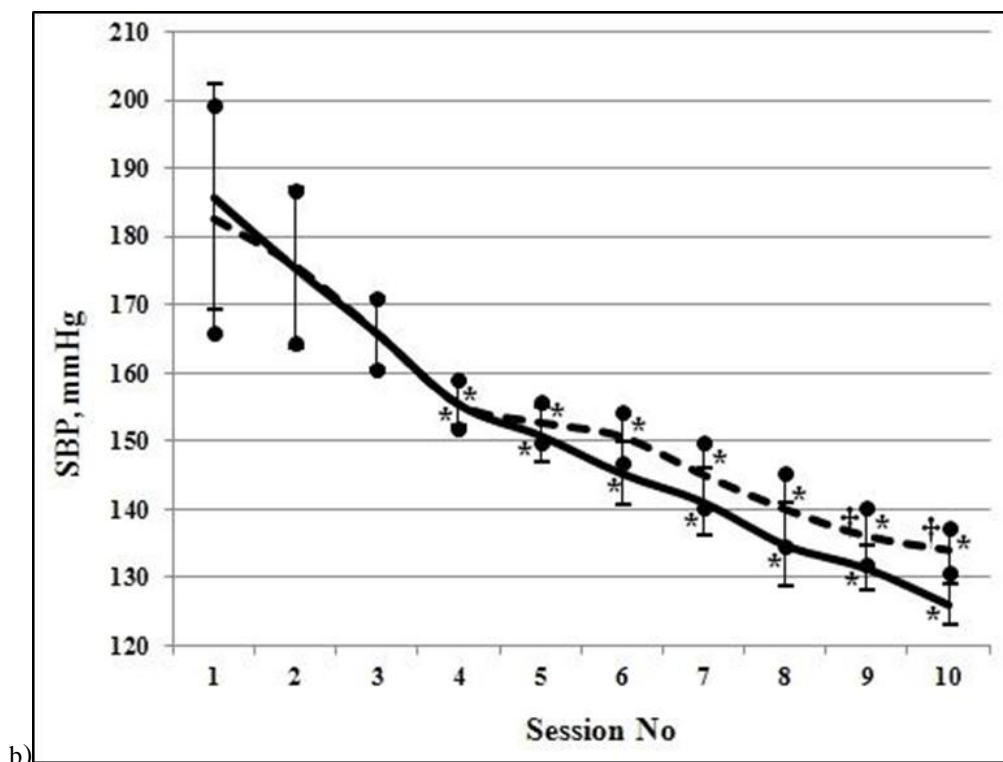
Note: — - BFB group; - - - - comparison group; * - $P < 0,01$ in the series against the baseline values; † - $P < 0,01$ between series on the current session.

Fig. 2 shows changes of SBP mean values at I - III stages of AH. In BFB group degree of SBP reduction were significantly ($p < 0.01$)

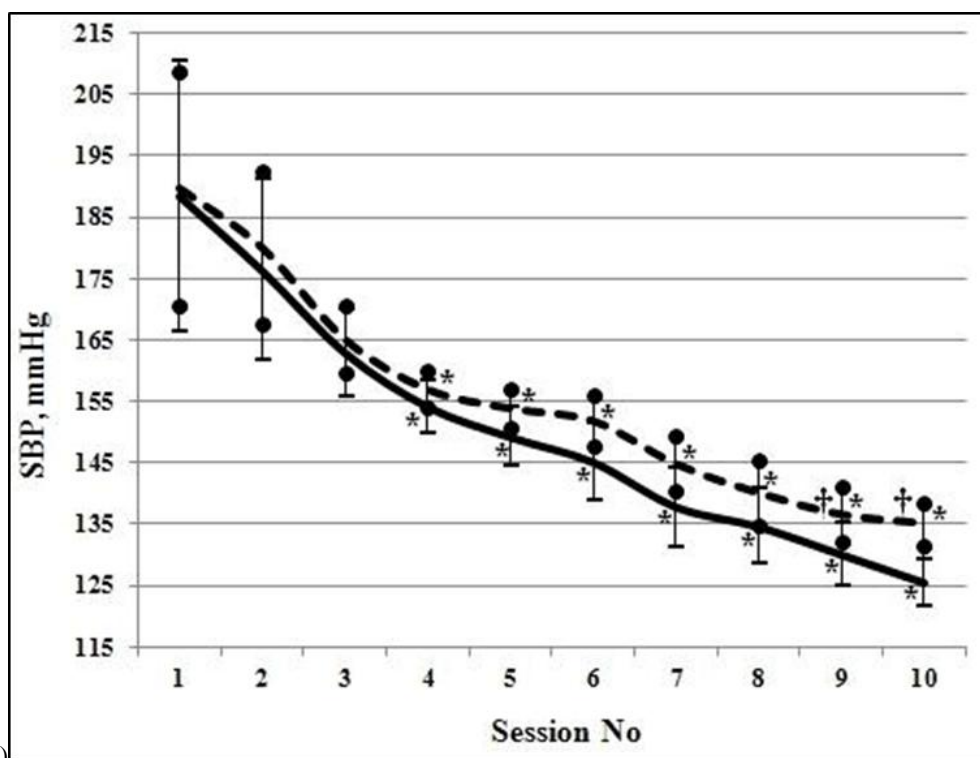
greater in 7 treatment day at I (Fig. 2a) and in 9 day - at II (Fig. 2b) and III (Fig. 2c) stages of AH against the comparison group.



a)



b)



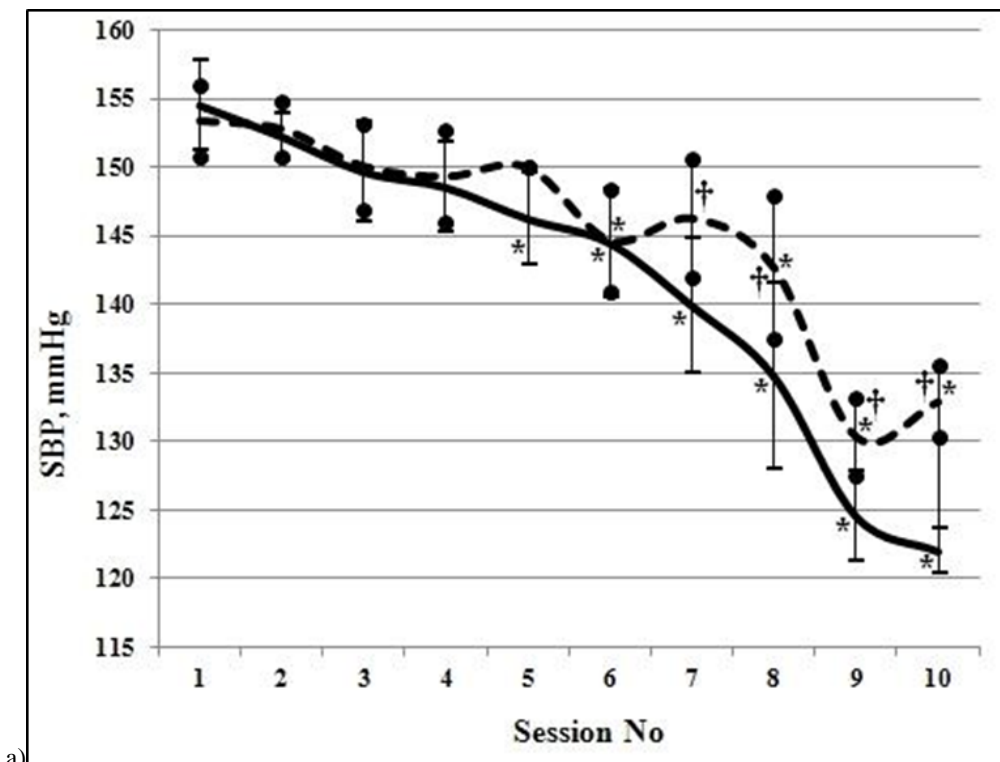
c)

Fig. 2. Changes of SBP mean values in patients with I (Fig. 2a), II (Fig. 2b) and III (Fig. 2c) stage of AH in groups of BFB and comparison at stages of observation

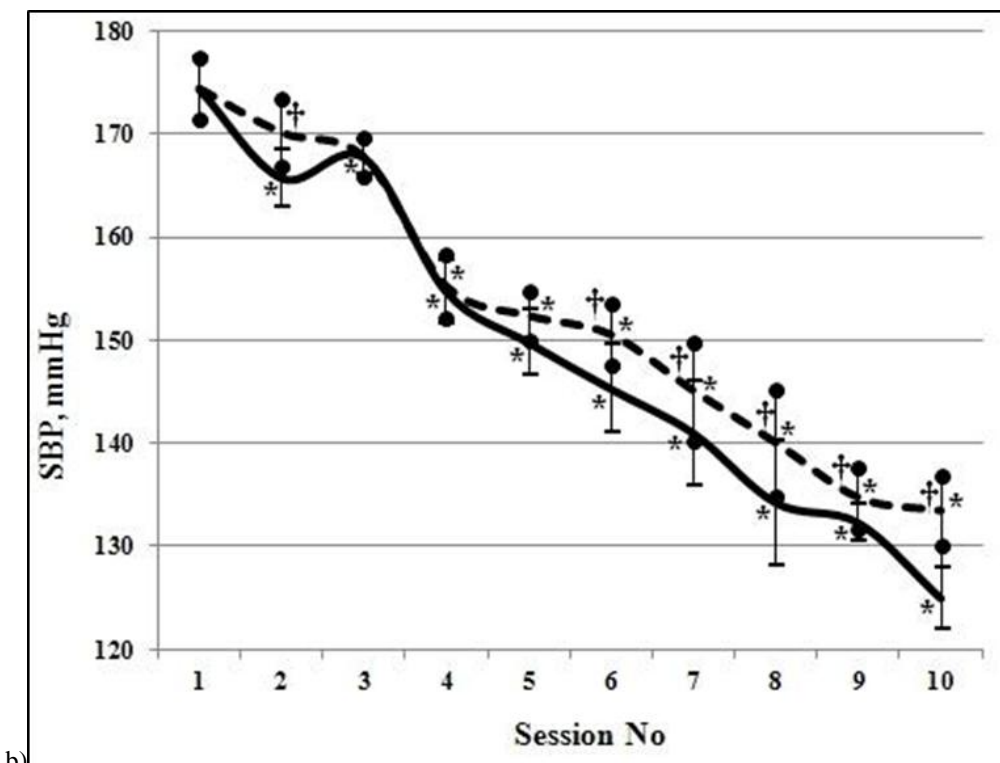
Note: ——— - BFB group; - - - - comparison group; * - $P < 0,01$ in the series against the baseline values; † - $P < 0,01$ between series on the current session.

Variability of SBP in groups of BFB and comparison depending on the degree of AH is shown in Fig. 3. Conducting of biofeedback sessions contributed to significantly ($p < 0.01$)

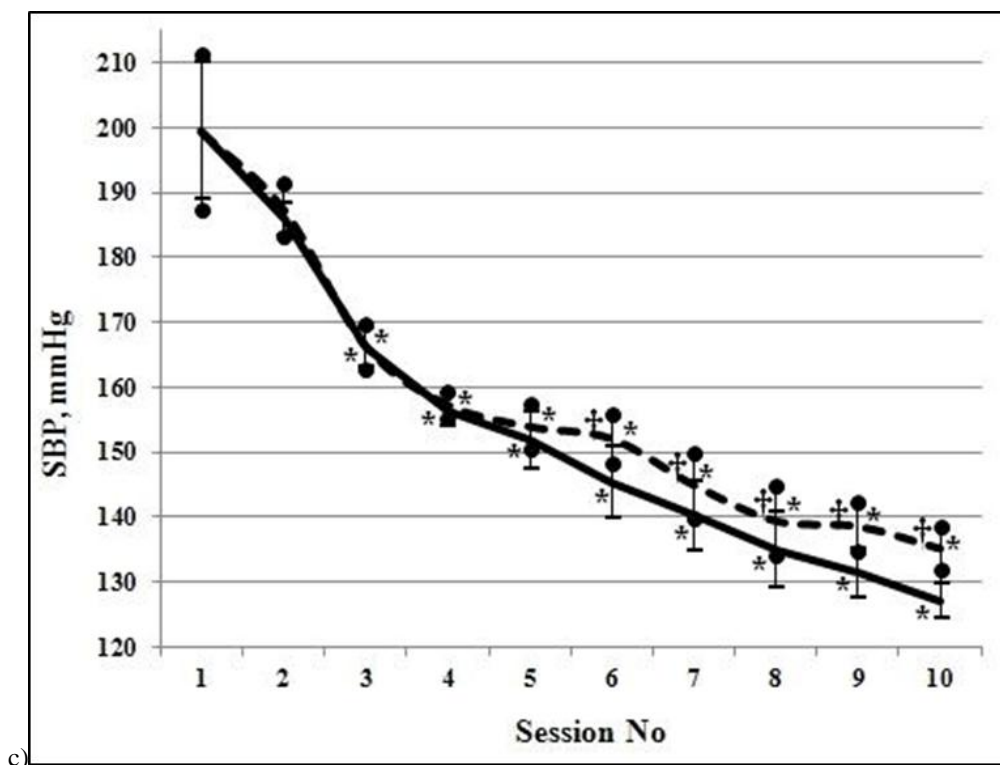
lower values of SBP at 7 session with 1 (Fig. 3a) and at 6 - with 2 (Fig. 3b) and 3 (Fig. 3c) degrees of AH against SBP values in the comparison.



a)



b)



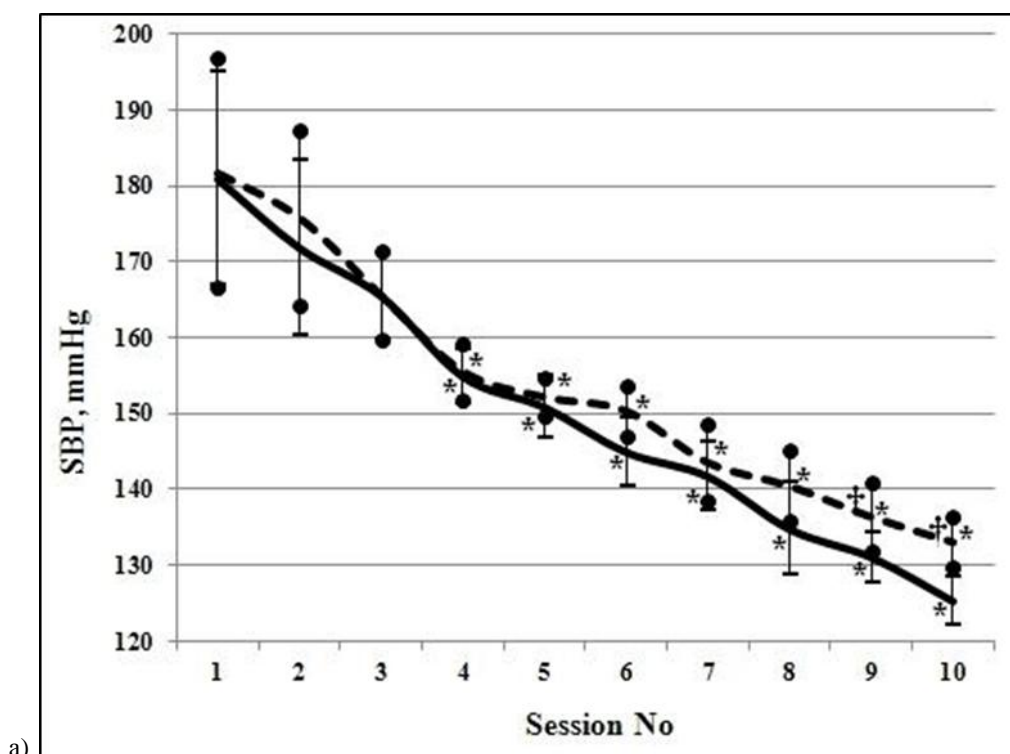
c)

Fig. 3. Changes of SBP mean values in patients with 1 (Fig. 3a), 2 (Fig. 3b) and 3 (Fig. 3c) degree of AH in groups of BFB and comparison at stages of observation

Note: —●— - BFB group; —■— - comparison group; * - $P < 0,01$ in the series against the baseline values; † - $P < 0,01$ between series on the current session.

Changes in the level of SBP in male and female patients with AH on the stages of observation are shown in Figure 4. The biofeedback sessions have led to significantly

($p < 0.01$) lower values of SBP in female patients at 9 (Fig. 4a) and in male patients at 7 (Fig. 4b) treatment day.



a)

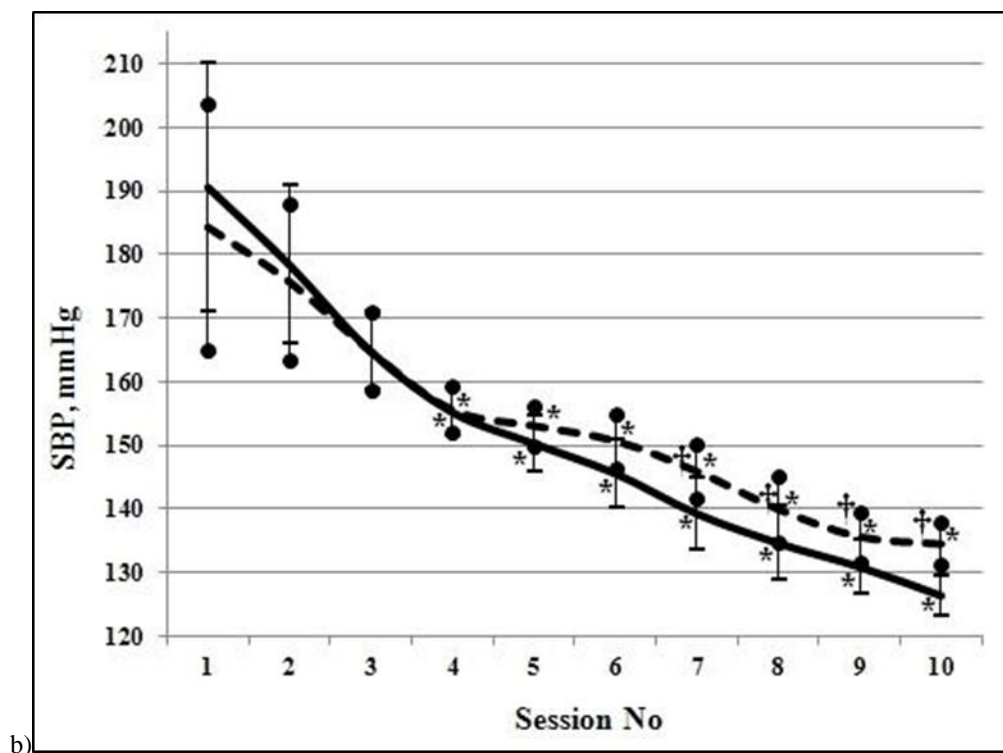
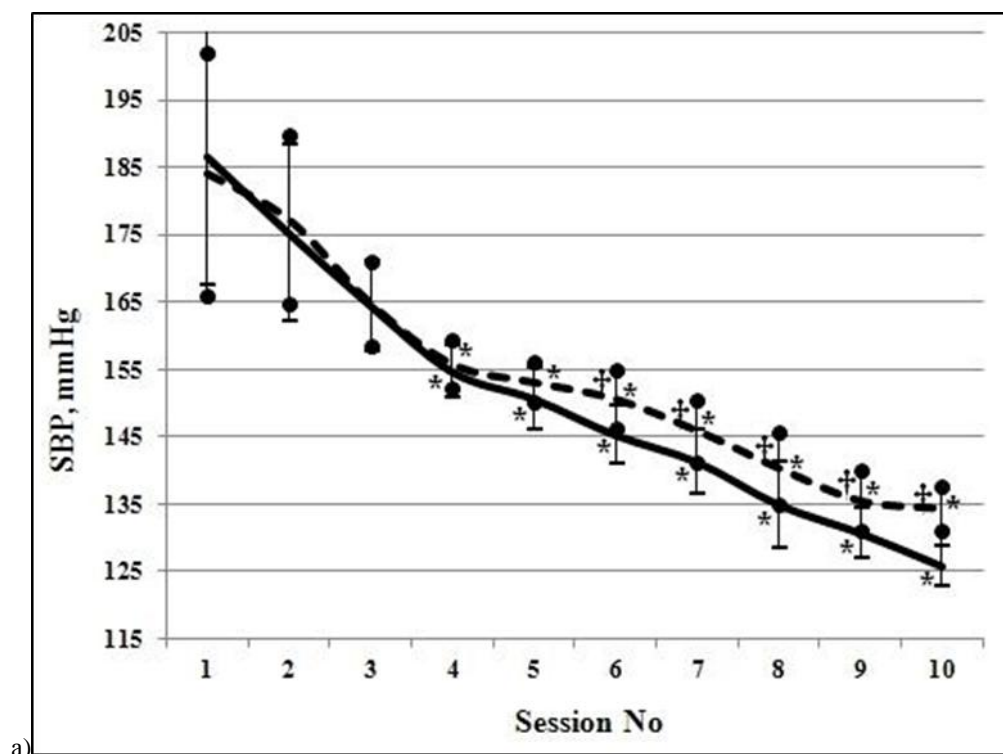


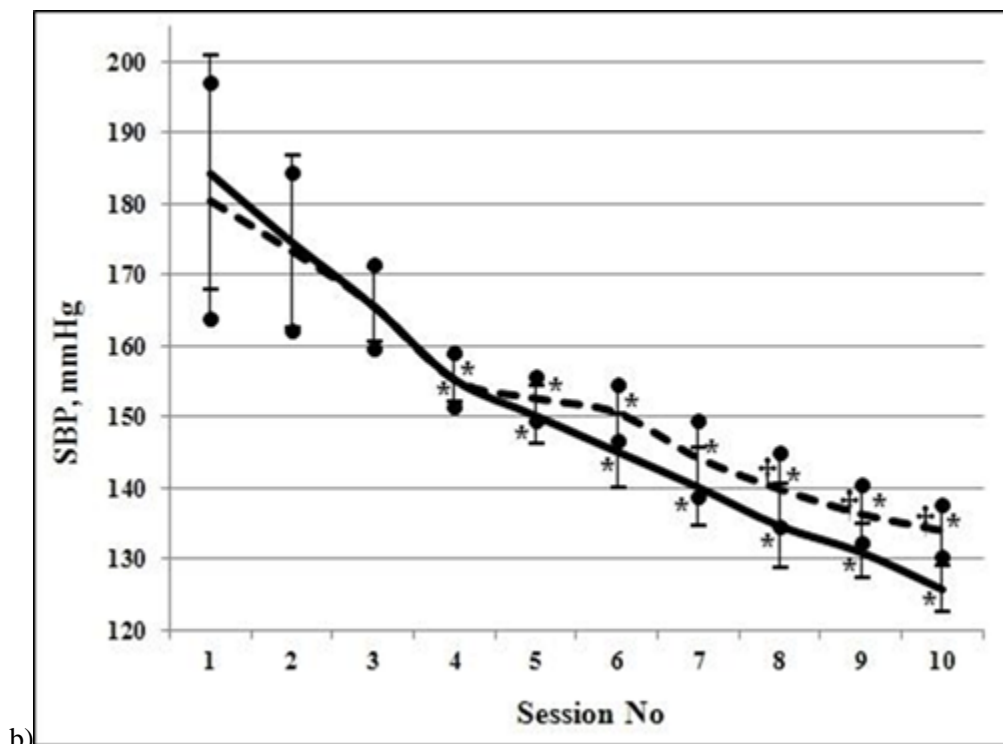
Fig. 4. Changes of SBP mean values in female (Fig. 4a) and male (Fig. 4b) patients in groups of BFB and comparison at stages of observation

Note: — - BFB group; - - - - comparison group; * - $P < 0,01$ in the series against the baseline values; † - $P < 0,01$ between series on the current session.

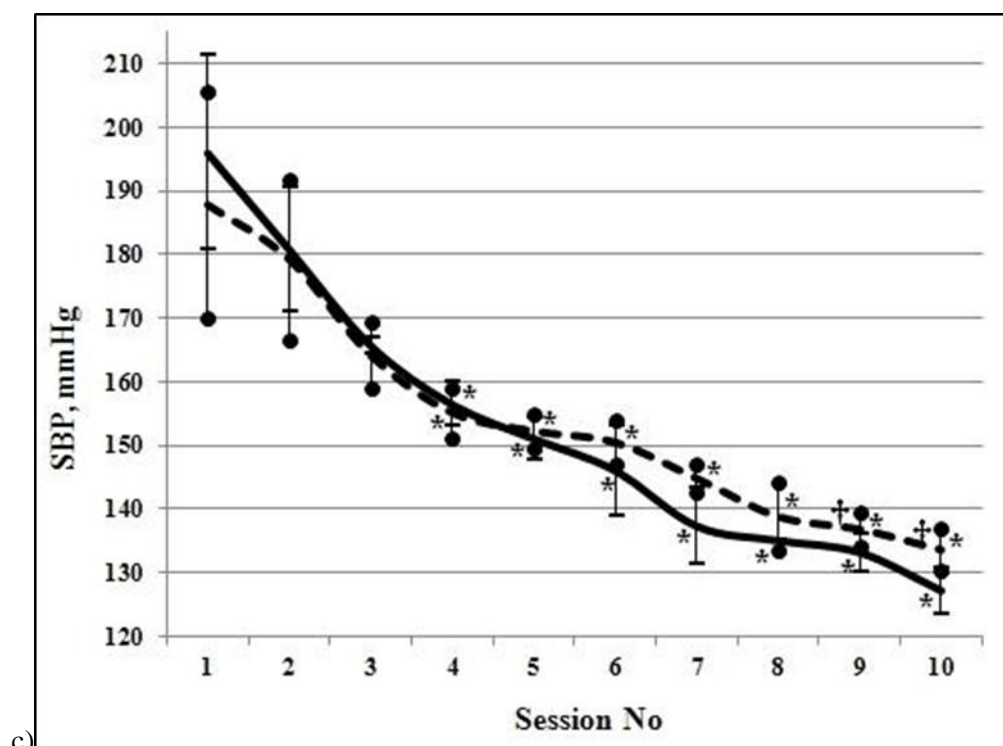
Changes of SBP in patients with AH in stages of the study in groups of BFB and comparison in different age groups are presented in Figure 5. Implementation of biofeedback sessions in the background of

standard medical therapy provides significantly ($p < 0.01$) better control of SBP in patients of mature age from 6 (Fig. 5a), elderly - from 8 (Fig. 5b) and old - from 9 (Fig. 5c) session as compared with that in the control group.





b)



c)

Fig. 5. Changes of SBP mean values in patients of mature (Fig. 5a), elderly (Fig. 5b) and old (Fig. 5c) age in groups of BFB and comparison at stages of observation

Note: ——— - BFB group; - - - - comparison group; * - P < 0,01 in the series against the baseline values; † - P < 0,01 between series on the current session.

Low in some patients manageability of SBP on the background of drug therapy [9] requires a search of new control methods including drug-free. BFB in the loop of PB and HRV is promising treatment for AH due to exposure to

the key link of the pathological condition - sympathovagal regulation [10].

In general population standard medical therapy allowed to reduce SBP by 26.6 %,

additional BFB sessions improved this index to 32.3 %.

The degree of SBP reduction in control group was 14 % for I, 26,6 % in II and 28.8 % for III stage of AH, and in the BFB group - 23.7 %, 32 % and 33.4 %, respectively. Probably, rising with AH stage increasing sympathovagal imbalance increases the sensitivity of regulatory systems to BFB [11], which was manifested in further decrease of SBP.

As for degrees of AH in patients of comparison group SBP decreased by 13.4 %, 23.5 % and 22.2 % with 1, 2 and 3 degrees, and in the BFB group – 21 %, 28.3 % and 36.3 %, respectively.

Standard medical therapy in the degree of SBP lowering was equally effective in male and female, but more significant in the BFB group, where it fell by 33.7 % and 30.8 % against 27 % and 26.8 %.

In patients of mature, middle and old age against the background of pharmacotherapy was noted almost same reduction of SBP (27 %, 25.7 % and 28.9 %, respectively). In the BFB sessions the reaction was much better - 32.6 %, 31.8 % and 35.1 %, respectively.

Our study confirmed [12] that the inclusion of BFB with the loop of PB and HRV to the therapy of patients with AH significantly increases its effectiveness against the isolated drug therapy regardless of the stage and degree of the disease, gender and age. The effectiveness of additional BFB sessions in the

loop of PB increases with the stage and degree of AH and is not associated with gender and age of the patients.

Obtained data allow to recommend this technique in clinical practice for patients with low SBP reduction during the treatment, and in AH generally as an additional therapy.

CONCLUSIONS

1. Biofeedback in the closed loop of paced breathing under the control of heart rate variability parameters can be used as a technology which increased the efficiency of the of systolic blood pressure control in arterial hypertension.

2. Efficiency of biofeedback sessions in closed loop of paced breathing under the control of heart rate variability parameters in systolic blood pressure control in arterial hypertension increases with the stage and grade of the disease and not depends on age and sex of patients.

3. Biofeedback in the closed loop of paced breathing under the control of heart rate variability parameters is especially useful in the arterial hypertension control in patients with inadequate reduction of systolic blood pressure.

PROSPECTS FOR FUTURE STUDIES

It is interesting to evaluate the effectiveness of in the closed loop of paced breathing under the control of heart rate variability parameters in control of diastolic blood and pulse pressure.

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A CONCOMITANT ANTIMICROBIAL ACTIVITY OF METHYLATED AND HALOGENATED GLUCOCORTICOSTEROIDS AGAINST MICROORGANISMS ISOLATED FROM THE SPUTUM OF CHILDREN WITH BRONCHIAL ASTHMA

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A concomitant antimicrobial activity of glucocorticosteroids (GCS) - prednisolone, methylprednisolone, dexamethasone, polcortolone, beclomethasone dipropionate, fluticasone propionate - for microorganisms isolated from the sputum of 135 children with bronchial asthma (BA) aged $11 \pm 0,12$ years was studied. In cultures was taken into account the number of isolated strains in the titer of bacteria (*S. aureus*, *S. pyogenes*, *E.coli*, *Pr. Mirabilis*, *Ps. Aeruginosa*, *C. albicans*) 10^3 U/ml and above, as well as yeast micromycetes (*C. albicans*). The antimicrobial activity of GCS was studied by double serial dilutions method with determining of minimum inhibitory concentration (MIC, mkg/ml) with the addition of these drugs in middle and low doses. Results were measured by nephelometric method according to changes of the optical medium density on the apparatus FEC-M with wavelength of 590 nm. The Antimicrobial activity of GCS was also analyzed depending on availability in their structure the methyl group CH_3 and/or halogens - Cl, F. The greatest antimicrobial activity had fluticasone propionate, which contains in its structure two F atoms and CH_3 , and the lowest activity - prednisolone. Low doses of GCS did not demonstrate bacteriostatic action and only average doses had an impact on growth of bacteria in the study. It is concluded that in children with BA should be implemented selectivity in the appointment of inhaled and oral GCS for long-term use in average doses.

KEY WORDS: bronchial asthma, antimicrobial activity, microorganisms, glucocorticosteroids

СУПУТНЯ АНТИМІКРОБНА АКТИВНІСТЬ МЕТИЛ- І ГАЛОГЕНУТРИМУЮЧИХ ГЛЮКОКОРТИКОСТЕРОЇДІВ ПО ВІДНОШЕННЮ ДО МІКРООРГАНІЗМІВ, ВИДІЛЕНИХ З МОКРОТИННЯ У ДІТЕЙ, ХВОРИХ НА БРОНХІАЛЬНУ АСТМУ

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Вивчено супутню антимікробну активність глюкокортикостероїдів (ГКС) - преднізолон, метилпреднізолон, дексаметазон, полькортолон, бекламетазону дипропионат, флутиказону пропіонату відносно мікроорганізмів, виділених з мокротиння 135 дітей, хворих на бронхіальну астму (БА) у віці $11 \pm 0,12$ років. У культурах враховувалася кількість виділених штамів в титрі бактерій (*S. aureus*, *S. pyogenes*, *E.coli*, *Pr. mirabilis*, *Ps. aeruginosa*, *C. albicans*) 10^3 Од/мл і вище, а також дріжджових мікроміцетів (*C. albicans*). Антимікробну активність ГКС вивчали методом дворазових серійних розведень з визначенням мінімальної інгібуючої концентрації з додаванням зазначених препаратів в середніх і низьких дозах. Результати оцінювали за змінами оптичної щільності середовища нефелометрично на апараті ФЕК-М при довжині хвилі 590 нм. Антимікробна активність ГКС аналізувалася також залежно від того, чи входили в їх структуру метильна група CH_3 і/або галогени - Cl, F. Результати показали, що найбільшу антимікробну активність мав флутиказона пропіонат, який у своїй структурі містить 2 атома F і CH_3 , а найменша активність спостерігається у преднізолоні, що не містить галогенів чи метильної групи. Також встановлено, що низькі дози ГКС не мають бактеріостатичної дії і тільки середньотерапевтичні дози впливають на ріст досліджуваних мікроорганізмів. Таким чином, у дітей з БА слід вибірково підходити до призначення інгаляційних та пероральних ГКС для тривалого застосування в середньотерапевтичних дозах.

КЛЮЧОВІ СЛОВА: бронхіальна астма, антимікробна активність, мікроорганізми, глюкокортикостероїди

СОПУТСТВУЮЩАЯ АНТИМИКРОБНАЯ АКТИВНОСТЬ МЕТИЛ - И ГАЛОГЕНСОДЕРЖАЩИХ ГЛЮКОКОРТИКОСТЕРОИДОВ В ОТНОШЕНИИ МИКРООРГАНИЗМОВ, ВЫДЕЛЕННЫХ ИЗ МОКРОТЫ ДЕТЕЙ, БОЛЬНЫХ БРОНХИАЛЬНОЙ АСТМОЙ

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Изучены сопутствующая антимикробная активность глюкокортикостероидов (ГКС) - преднизолон, метилпреднизолон, дексаметазон, полкортолон, бекламетазона дипропионат, флутиказона пропионата - в отношении микроорганизмов, выделенных из мокроты 135 больных бронхиальной астмой (БА) детей в возрасте $11 \pm 0,12$ лет. В культурах учитывалось количество выделенных штаммов в титре бактерий (*S. aureus*, *S. pyogenes*, *E.coli*, *Pr. mirabilis*, *Ps. aeruginosa*, *C. albicans*) 10^3 Ед/мл и выше, а также дрожжевых микромицетов (*C. albicans*). Антимикробную активность ГКС изучали методом двукратных серийных разведений с определением минимальной ингибирующей концентрации с добавлением указанных препаратов в средних и низких дозировках. Результаты оценивали по изменению оптической плотности среды нефелометрически на аппарате ФЭК-М при длине волны 590 нм. Антимикробная активность ГКС анализировалась также в зависимости от того, входили ли в их структуру метильная группа CH_3 и/или галогены - Cl, F. Наибольшей антимикробной активностью обладал флутиказона пропионат, который в своей структуре содержит 2 атома F и CH_3 , а наименьшей активностью - преднизолон. Низкие дозы ГКС не оказывали бактериостатического действия и только среднетерапевтические влияли на рост исследуемых микроорганизмов. Делается вывод, что у детей с БА следует избирательно подходить к назначению ингаляционных и пероральных ГКС для длительного применения в среднетерапевтических дозах.

КЛЮЧЕВЫЕ СЛОВА: бронхиальная астма, антимикробная активность, микроорганизмы, глюкокортикостероиды

INTRODUCTION

One of leading places in the treatment of bronchial asthma (BA) is given to inhaled glucocorticosteroids (GCS), prescription of which as universal anti-inflammatory drugs is the foundation of basic therapy [1, 2, 3]. GCS provide comprehensive pharmacological effect, which is caused by their influence on the functional activity of the genetic apparatus of cells, suppression of the synthesis and activity of cytokines that stimulate the processes of differentiation, maturation of bone marrow eosinophilic granulocytes and mast cells by blocking the formation of IgE, the suppression of late asthmatic reaction, reduction of bronchial hyperreactivity. However, some studies have shown that in patients receiving inhaled GCS during long time can occur pathogens colonization that can lead to changes in the disease course, the persistence of pathogenic organisms, forming a vicious circle that makes effective treatment in this group of patients very difficult [4, 5, 6].

OBJECTIVE

The aim of this study was to investigate the antimicrobial activity of average and low doses of GCS, the structure of which includes methyl

group and halogens, on microorganisms isolated from the sputum of children with BA.

MATERIALS AND METHODS

To determine the antimicrobial activity of GCS (prednisolone, methylprednisolone, dexamethasone, polcortolone, beclomethasone dipropionate, fluticasone propionate) was conducted microbiological examination of sputum from 135 children with BA in the period of exacerbation in all forms of the disease (atopic, non-atopic, mixed). The diagnosis of BA was established according to the recommendations of GINA (2012) [7]. Patients' age was from 5 to 14 years, the average was $11 \pm 0,12$ years. Sputum culture tests were carried out on a nutrient medium - Mueller-Hinton agar by the standard technique [8]. In cultures was taken into account the number of isolated strains of bacteria in the titer 10^3 U/ml and above, as well as yeast micromycetes (*C. albicans*). The antimicrobial activity of GCS was studied by double serial dilutions method with determining of minimum inhibitory concentration (MIC, mkg/ml) with the addition of these drugs in average and low doses recommended by GINA (2012) for the treatment of BA with the assessment of their impact on the growth of microorganisms (tab. 1).

Table 1

Doses of GCS which used for determining the minimum inhibitory concentration for isolated microorganisms from the children with BA sputum in the period of exacerbation

Drug	Doses	
	Low doses	Middle doses
Prednisolone	0,1-0,2 mg/kg/day	0,5-1 mg/kg/day
Methylprednisolone	0,1 -0,2 mg/kg/day	0,5-1 mg/kg/day
Dexamethasone	0,01-0,02 mg/kg/day	0,05-0,1 mg/kg/day
Beclomethasone dipropionate	100-250 mkg/day	250-500 mkg/day
Fluticasone propionate	50-100 mkg/day	100-250 mkg/day
Polcortolone	0,02-0,05 mg/kg/day	0,1-0,2 mg/kg/day

Tube containing clean growth medium served as a control. To each tube was added 0.05 ml of saline containing 10^6 ml of the microbial cells. The tubes were incubated for 16-18 hours at the temperature of 37°C (or before the appearance of bacterial growth in the control tube). Results are taken into

account by nephelometric method according to changes of the optical medium density on the apparatus FEC-M with wavelength of 590 nm [9]. Antimicrobial activity of GCS was also analyzed depending on availability in their structure methyl group CH_3 and/or halogens - Cl, F (tab. 2)

Table 2

GCS drugs depending on availability in their structure of the methyl group (CH_3) and/or halogens

GCS	The number of methyl groups (CH_3) and / or halogens (F, Cl)
Prednisolone	-
Methylprednisolone	CH_3
Dexamethasone	F
Polcortolone	F
Beclomethasone dipropionate	Cl+ CH_3
Fluticasone propionate	2F+ CH_3

Statistical analysis of MIC results for GCS was conducted with the help of applications Excel, Statgraphics-5 with the definition of the mean value (M), standard error of the mean (m). The reliability between the MIC means of drugs to selected microorganisms in comparison with prednisolone was estimated by parametric statistical methods (Student's t test).

RESULTS AND DISCUSSION

Study showed that in children with BA sputum of in all forms of the disease were determined following organisms: *S. aureus*, *S. pyogenes*, *E.coli*, *Pr. mirabilis*, *Ps. aeruginosa*, *C. albicans* (tab. 3).

Table 3

Microview of sputum from children with BA depending on the form of disease (%)

Microorganism	Total (n=135)	Form of BA		
		Atopic (n=44)	Non-atopic (n=45)	Mixed (n=46)
<i>S. aureus</i>	14,1	9,1	17,9	15,2
<i>S. pyogenes</i>	10,4	6,8	11,1	13,1
<i>E.coli</i>	10,4	11,4	8,9	10,9
<i>Pr. mirabilis</i>	9,6	13,6	8,9	6,5
<i>Ps. aeruginosa</i>	14,8	16,0	13,3	15,2
<i>C. albicans</i>	11,1	18,2	4,4	10,9

In 29.6 % of children with BA in the sputum were seeded associations of *S. aureus* with *S. pyogenes*, *E. coli*, *Pr. mirabilis*, *Ps. aeruginosa*.

In determining the antimicrobial activity of GCS it was found that low-dose drugs recommended by GINA for patients with BA do not exert a bacteriostatic action on microorganisms isolated from the sputum of children with BA. Only in average doses appears inhibitory effect of GCS on the growth of microorganisms. As indicated in table 4, the worst antimicrobial effect had prednisolone and the most effective was fluticasone propionate. This drug has the pronounced effect on all types of microorganisms and only one that showed antimicrobial activity against *C. albicans*. It should be noted that the prednisolone and methylprednisolone didn't show activity against *P. aeruginosa*.

To a certain extent, the antimicrobial activity of studied GCS may be associated with

features of the chemical structure of the drug. Thus, prednisolone, which in its composition does not contain methyl group or halogens, showed minimal antimicrobial activity. In process of chemical structure complication due to the presence of methyl group (CH_3) and/or Cl, F was marked augmentation of GCS antimicrobial activity. Thus, in comparison with antimicrobial activity of prednisolone, methylprednisolone (contains CH_3 group) was in 1.7 times more active to *S. aureus* and *S. pyogenes* ($p < 0.05$), in 1.5 times - to *Pr. mirabilis* ($p < 0.05$) and in 1.2 times - to *E. coli* ($P < 0.05$). Dexamethasone (which includes F) exceeded the activity of prednisolone to *S. aureus* and *S. pyogenes* in 2.5 times ($p < 0.05$) to *Pr. mirabilis* - in 3.7 times ($p < 0.05$), and to *E. coli* - in 1.2 times ($p < 0.05$). The same level and spectrum of antimicrobial activity was marked for halogen-containing beclomethasone dipropionate and polcortolone.

Table 4

Antimicrobial activity of glucocorticoid drugs against the microflora isolated from the sputum of children with BA in the period of exacerbation in serially diluted minimal inhibitory concentration (MIC), ($M \pm m$) mcg/ml

GCS drugs in average doses	Antimicrobial activity in serial dilutions of MIC (mcg / ml)					
	<i>S. aureus</i>	<i>S. pyogenes</i>	<i>E. coli</i>	<i>Pr. mirabilis</i>	<i>Ps. aeruginosa</i>	<i>C. albicans</i>
Prednisolone	483,2 ± 11,3	491,3 ± 11,9	532,6 ± 12,4	391,2 ± 12,8	-	-
Methylprednisolone	284,6 ± 17,3*	283,2 ± 16,5*	393,5 ± 11,6*	253,9 ± 10,6*	-	-
Dexamethasone	192,5 ± 14,8*	190,6 ± 15,2*	398,2 ± 22,5*	130,7 ± 18,7*	164,3 ± 9,8	-
Polcortolone	228,7 ± 20,2*	245,8 ± 20,9*	386,3 ± 9,8*	167,8 ± 11,2*	170,4 ± 11,6	-
Beclomethasone dipropionate	234,3 ± 18,9*	242,1 ± 17,8*	371,4 ± 14,3*	142,5 ± 16,5*	172,6 ± 13,9*	-
Fluticasone propionate	109,8 ± 7,5*	110,5 ± 8,3*	120,5 ± 6,7*	93,4 ± 5,8*	141,2 ± 11,8*	393,6 ± 21,9

Notes: * - $p < 0,05$ - indicators of MIC drugs to isolated microorganisms in comparison with indicators for prednisone

At the same time, fluticasone propionate due to two F atoms and CH_3 exceeded activity of prednisolone to *S. aureus*, *S. pyogenes*, *P. mirabilis* and *E. coli*, respectively, in 4.4 - 5.2 times ($p < 0.05$).

Our findings are consistent with Derom E. study, which shows that for GCS series (prednisolone, beclomet, dexamethasone) inherent ability to provide bacteriostatic effect to *S. aureus* and *E. coli* in adult patients with BA and during prolonged passaging in

the presence of GCS minimal dose cultural properties of these organisms was stimulated [10]. However, our results did not show the possibility of GCS low doses to enhance the growth of microorganisms. Furthermore, in conditions of prolonged use, especially irrational schemes, GCS can act as a formation factor of microorganisms' drug resistance [5, 11, 12] The analysis in system «chemical structure - biological effect» demonstrates that concomitant antimicrobial

activity in the studied GCS drugs depends on the availability in their chemical structure methyl groups and halogens. Given this, it is possible, regardless of the clinical form and severity of BA in children, to find the selective approach to the appointment of inhaled and oral GCS for long-term use in average therapeutic doses.

CONCLUSIONS

1. Glucocorticosteroids have the concomitant antimicrobial activity, the severity of which depends on the availability in their chemical structure methyl and halogens compounds.

2. Concomitant antimicrobial potential increases in difluoromethanecontaining fluticasone propionate, in halogencontaining dexamethasone, polcortolone and beclomethasone dipropionate against microorganisms isolated from the sputum of children with BA.

PROSPECTS FOR FUTURE STUDIES

The study of antimicrobial activity of methyl- and halogencontaining GCS is a promising scientific trend at drug selecting for treatment of BA in children, predicting the development of disease remission and determining the duration of the treatment.

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MORPHOMETRIC INDICATORS OF AN ORBIT AT ADULTS IN CONNECTION WITH TYPES OF CRANIUM

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The norm of morphometric indicators of bone structures of an orbit for population of 96 people at the age of $48,6 \pm 3,2$ years without pathology of craniofacial area is established by method of a computer tomography. Means, confidence intervals ($p = 0,05$), correlation and reliability of distinctions in morphometric indicators of a skull and an orbit by groups on types of cranium are defined. In frequency distribution of the studied population by types of cranium brachiocephalic people are 63 %, dolichocephalic – 27% and mesocephalic – 10 %. In groups by types of cranium among linear indicators of an orbit length of a medial wall statistically reliable decreases from dolichocephals to brachiocephals, length of lateral wall, orbital floor and roof and also orbital breadth – from mesocephals to brachiocephals. Orbital height between groups' types of cranium reliable does not differ. An angle between medial and lateral walls of orbit statistically reliable increases from dolichocephalic persons to brachiocephalic. The interrelation of changes of an angle of orbital entrance inclination and types of cranium is not observed. The number of statistically significant correlations between morphometric indicators of an orbit increases from dolichocephals to brachiocephals at the absence of a reliable difference between them. Average degree correlation is noted only between orbital breadth and lengths of medial wall and orbital floor; orbital depth and lengths of the orbital floor and roof; between lengths of the orbital floor and roof – at brachiocephals, and also between lengths of the orbital floor and roof – at dolichocephals and mesocephals. The conclusion is drawn that when planning reconstructive operations at bone structures of an orbit it is necessary to consider the available distinctions in length of lateral wall, orbital roof and floor, height and breadth and value of an angle between medial and lateral walls by types of cranium.

KEY WORDS: orbit, morphometry, types of cranium, cranial index

МОРФОМЕТРИЧНІ ПОКАЗНИКИ ОЧНОЇ ЯМКИ ДОРΟΣЛИХ ЛЮДЕЙ У ЗВ'ЯЗКУ З КРАНІОТИПАМИ

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Встановлена норма морфометричних показників кісткових структур очної ямки на вибірці з 96 чоловік у віці $48,6 \pm 3,2$ року без патології краніофасіальної області методом комп'ютерної томографії. Визначені середні значення, довірчі інтервали ($p = 0,05$), взаємозв'язок і вірогідність відмінностей в морфометричних показниках черепа і орбіти в групах за краніотипами. У частотному розподілі дослідженої вибірки за краніотипами брахіцефали складають 63 %, мезоцефали – 27 % і доліхоцефали – 10%. В групах краніотипів серед лінійних показників очної ямки довжина медіальної стінки статистично вірогідно зменшується від доліхоцефалів до брахіцефалів, довжина латеральної, верхньої і нижньої стінок, а також ширина входу в очну ямку – від мезоцефалів до брахіцефалів. Висота входу в очну ямку між групами краніотипів вірогідно не розрізняється. Кут між медіальною і латеральною стінками очної ямки вірогідно збільшується від доліхоцефалів до брахіцефалів. Взаємозв'язок змін кута нахилу входу в очну ямку і краніотипів не проявляється. Число статистично значущих взаємозв'язків між морфометричними показниками очної ямки збільшується від доліхоцефалів до брахіцефалів за відсутності вірогідної різниці між ними. Середня кореляція відзначається тільки між шириною входу і довжиною медіальної і нижньої стінок, глибиною і довжиною нижньої і верхньої стінок, довжиною верхньої і нижньої стінок очної ямки – у брахіцефалів, а також між довжиною нижньої і верхньої стінок – у доліхоцефалів і мезоцефалів. Зроблено висновок, що при плануванні реконструктивних операцій на кісткових структурах очної ямки слід враховувати наявні відмінності між краніотипами по довжині латеральної, верхньої і нижньої стінок, ширині і висоті входу в очну ямку і величині кута між медіальною і латеральною стінками.

КЛЮЧОВІ СЛОВА: очна ямка, морфометрія, краніотипи, черепний індекс

МОРФОМЕТРИЧЕСКИЕ ПОКАЗАТЕЛИ ОРБИТЫ ВЗРОСЛЫХ ЛЮДЕЙ В СВЯЗИ С КРАНИОТИПАМИ

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Установлена норма морфометрических показателей костных структур орбиты на выборке из 96 человек в возрасте $48,6 \pm 3,2$ года без патологии краниофациальной области методом компьютерной томографии. Определены средние значения, доверительные интервалы ($p = 0,05$), взаимосвязь и достоверность различий в морфометрических показателях черепа и орбиты в группах по краниотипам. В частотном распределении исследованной выборки по краниотипам брахицефалы составляют 63 %, мезоцефалы – 27 % и долихоцефалы – 10 %. В группах краниотипов среди линейных показателей орбиты длина медиальной стенки орбиты статистически достоверно уменьшается от долихоцефалов к брахицефалам, длина латеральной, верхней и нижней стенок, а также ширина входа в орбиту – от мезоцефалов к брахицефалам. Высота входа в орбиту между группами краниотипов достоверно не различается. Угол между медиальной и латеральной стенками орбиты статистически достоверно увеличивается от долихоцефалов к брахицефалам. Взаимосвязь изменений угла наклона входа в орбиту и краниотипов не проявляется. Число статистически значимых взаимосвязей между морфометрическими показателями орбиты увеличивается от долихоцефалов к брахицефалам при отсутствии достоверной разницы между ними. Средней степени корреляция отмечается только между шириной входа и длинами медиальной и нижней стенок, глубиной и длиной нижней и верхней стенок, длиной верхней и нижней стенок орбиты – у брахицефалов, а также между длиной нижней и верхней стенок – у долихоцефалов и мезоцефалов. Сделан вывод, что при планировании реконструктивных операций на костных структурах орбиты следует учитывать имеющиеся различия в краниотипах по длине латеральной, верхней и нижней стенок, ширине и высоте входа в орбиту и величине угла между медиальной и латеральной стенками.

КЛЮЧЕВЫЕ СЛОВА: орбита, морфометрия, краниотипы, черепной индекс

INTRODUCTION

Type of person's cranium, along with age and sex, is one of the factors of variability of morphometric parameters of the skull and its anatomical structures, including orbit. That is why its definition serves an important prerequisite for the planning of surgical reconstructive operations in the orbital zone. Available literature data [1, 2] mainly deal with sex-age aspects of individual variability of bone structures of the orbit. In [3] the assessment of orbital height and breadth is carried out, and in [4] linear indicators of orbits are investigated in connection with a shape of a face. The insufficient attention which is paid to influence of the main types of cranium on individual variability of the sizes of bone structures of an orbit causes necessity of this research.

OBJECTIVE

The objective of the study is to establish quantitative standards and reveal anatomical differences in the morphometric parameters of the orbital bone structures by types of cranium defined due to the cranial index.

MATERIALS AND METHODS

The object of study – 96 persons at the age of 21 to 74 years (mean age $48,6 \pm 3,2$ years) without pathology of craniofacial area investigated in Donetsk diagnostic center with their consent.

For morphometric studies multiscan computed tomography (CT) performed with use of Brilliance CT 64 (Philips) apparatus in the supine position with arms along the body. After selecting the baseline scan regime, scans were made with a thickness of 5 mm, followed by reconstruction up to 2 mm. As a post-processing of data the VRT (volume reconstruction) mode was used to improve visualization of bone structures.

In the received CT-scans according to [5-7] length of orbital walls from an opening of the optic nerve channel, orbital height and breadth, angle of orbital entrance inclination and angle between medial and lateral walls were measured. For definition of types of cranium due to [8] width and length of a skull were measured and the cranial index as a width divided by length expressed as a percentage was calculated. Thus a row of craniometrical points was used: ectoconchion (ec), eurion (eu), glabella (g), infraorbitale (oi), maxillo-

frontale (mf), supraorbitale (os), opisthocranium (op), point on the optic foramen (Of) (fig. 1).

According to value of the index each case belonged to one of three types of cranium: dolichocephalic (a cranial index is less than 74,9 %); mesocephalic (value of index is from 75,0 % to 79,9 %) and brachiocephalic (a cranial index exceeds 80,0 %). In defined groups by types of cranium statistical parameters of linear and angular morphometric indicators of orbits were estimated.

Statistical processing of the obtained data was carried out with use of the license software package of Microsoft Excel 2010© according to recommendations [9-10] in the following

sequence: verification of data of each selection on a normality by means of criterion χ^2 ; calculation of a mean, maximum and minimum values, skewness, kurtosis, variation coefficient Cv, standard errors of means and variation coefficients; definition of a confidence intervals of mean and variation coefficient. An assessment of the statistical significance of differences of means was done with use of t-criterion in case of a normal distribution of populations or Mann-Whitney's criterion – otherwise. Variability of values admitted weak if Cv did not exceed 10 %, average – if Cv was 11-25 %, considerable – at Cv > 25 %.

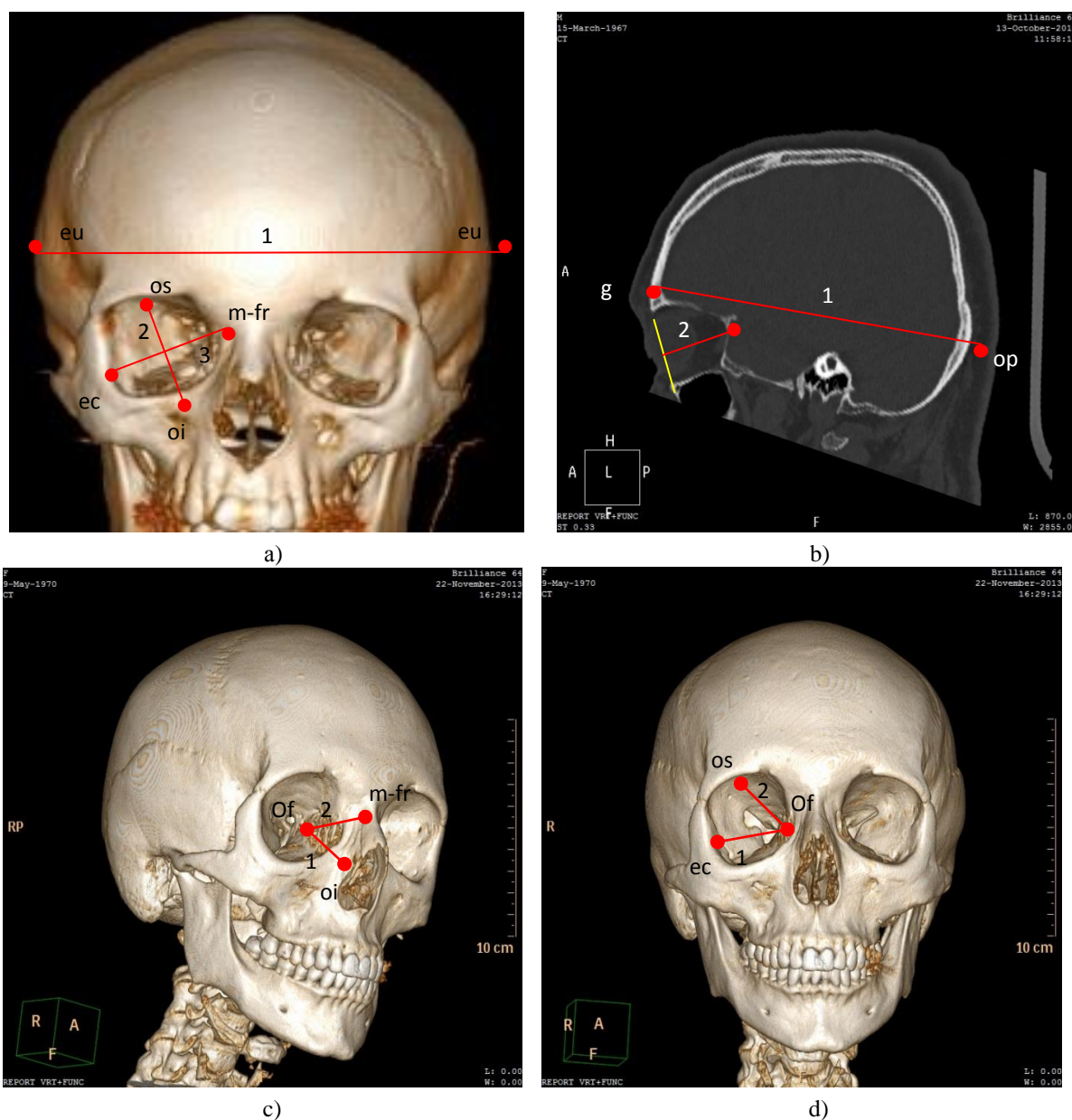


Fig. 1. Linear indices of a skull and an orbit:

- a) 1 – skull width; 2 – orbital height, 3 – orbital breadth; b) 1 – skull length; 2 – orbital depth;
- c) 1 – orbital floor length; 2 – medial wall length; d) 1 – lateral wall length; 2 – orbital roof length.

The correlation analysis was carried out on the basis of calculation of Pearson's coefficient of correlation and the subsequent assessment of the reliability of difference of received coefficients from zero, calculation of a confidence interval of their average values, assessment of reliability of difference between statistically significant coefficients of correlation.

Differences of means and correlation coefficients admitted reliable at $p \leq 0,05$.

RESULTS AND DISCUSSION

The frequency distribution of the studied population into groups by types of cranium is shown at fig. 2.

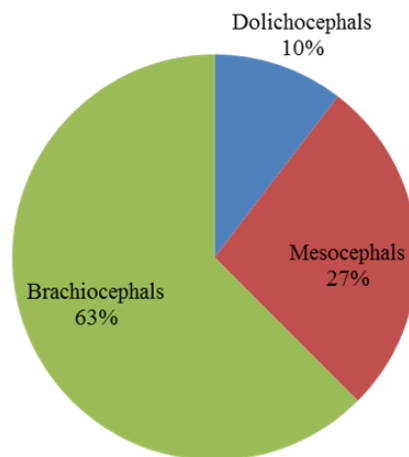


Fig. 2. Population distribution by types of cranium

The main groups are brachycephals which 6 times exceed the number of dolichocephals and 2.3 times – mesocephals.

In tab. 1 statistical parameters of linear indicators are specified by groups due to the cranial index.

Table 1

Linear morphometric indicators of an orbit in groups by types of cranium according to a cranial index*

Indicator, measurement unit	Type of cranium **	Descriptive statistics					
		M ± σ	Min	Max	As	E	Cv, %
Medial wall length, mm	D	46,1 ± 1,0	43,3	48,3	-0,4	0,9	3,0
	M	44,4 ± 0,7	41,6	46,7	-0,4	-1,1	3,7
	B	42,8 ± 0,5	38,6	47,6	0,3	0,3	4,4
Lateral wall length, mm	D	41,0 ± 0,6	39,4	42,4	-0,3	0,1	2,1
	M	41,4 ± 0,4	39,1	42,7	-0,9	0,5	2,2
	B	40,6 ± 0,2	38,7	43,2	0,3	0,1	2,3
Orbital floor length, mm	D	40,6 ± 0,5	39,9	41,5	0,5	-1,8	1,5
	M	40,3 ± 0,3	38,8	41,6	-0,1	0,6	1,6
	B	39,3 ± 0,3	36,1	41,4	-0,5	0,2	2,8
Orbital roof length, mm	D	41,1 ± 0,6	40,1	42,6	0,7	-0,4	2,1
	M	41,2 ± 0,4	39,4	43,0	0,0	-0,7	2,3
	B	40,4 ± 0,2	38,0	42,2	-0,4	-0,1	2,4
Orbital breadth, mm	D	39,7 ± 0,4	38,1	44,0	-1,3	-1,1	1,6
	M	39,7 ± 0,4	37,8	41,3	-0,2	-0,9	2,4
	B	38,9 ± 0,2	36,5	41,2	-0,3	0,4	2,5
Orbital height, mm	D	34,4 ± 0,5	33,6	35,9	1,2	1,1	2,0
	M	34,2 ± 0,3	33,1	36,0	0,8	-0,4	2,4
	B	34,0 ± 0,3	32,3	36,5	0,3	-0,6	3,0
Orbital depth, mm	D	45,1 ± 1,1	42,5	47,9	0,3	0,3	3,4
	M	43,2 ± 0,7	40,2	47,5	0,6	0,3	4,0
	B	41,7 ± 0,6	36,9	46,7	0,4	-0,2	5,6

* hereinafter in tables – M – mean, σ – standard deviation, t – rate of t-distribution for 95% two-sided critical region and for the corresponding number of degrees of freedom; M ± σt – confidence interval; Min and Max – minimum and maximum value of indicators in a population, As – skewness, E – kurtosis, Cv – variation coefficient;

** – D – dolichocephalic group; M – mesocephalic group, B – brachiocephalic group.

Variability of linear indicators of orbit is low and demonstrates an increase tendency from group of dolichocephalic persons to group of brachiocephalic. Differences between all groups are insignificant for orbital height.

There are significant distinctions between groups of mesocephals and brachiocephals in length of lateral wall, orbital roof and floor and orbital breadth – these indicators are higher in group of mesocephals (fig. 3).

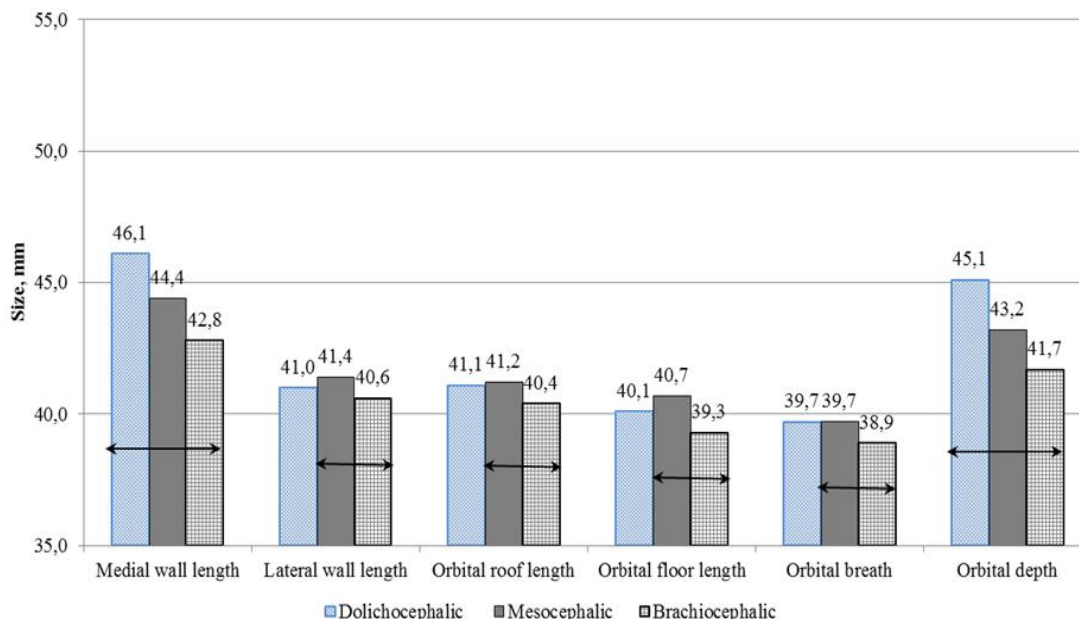


Fig. 3. Linear indicators with reliable differences between groups by a cranial index

In tab. 2 statistical parameters of angular indicators of an orbit are given by groups according to the types of cranium.

Table 2

Angular morphometric indicators of an orbit in groups by types of cranium according to a cranial index

Indicator, measurement unit	Type of cranium	Descriptive statistics					
		M ± σ	Min	Max	As	E	Cv, %
Angle of orbital entrance inclination,	D	10,6 ± 1,3	7,8	13,1	0,0	-1,1	17,0
	M	10,6 ± 0,7	7,6	13,2	-0,3	-1,1	16,6
	B	10,2 ± 0,5	6,8	13,7	-0,1	-1,1	18,4
Angle between medial and lateral walls,	D	48,1 ± 2,4	43,9	54,0	0,6	-0,8	7,1
	M	51,0 ± 2,0	41,5	61,1	-0,1	-0,5	9,8
	B	53,0 ± 1,0	41,4	58,9	-0,8	0,6	7,0

Variability of angular indicators unlike linear is higher. Statistically reliable distinctions between groups by types of

cranium are noted only in values of the angle between medial and lateral walls of an orbit (fig. 4).

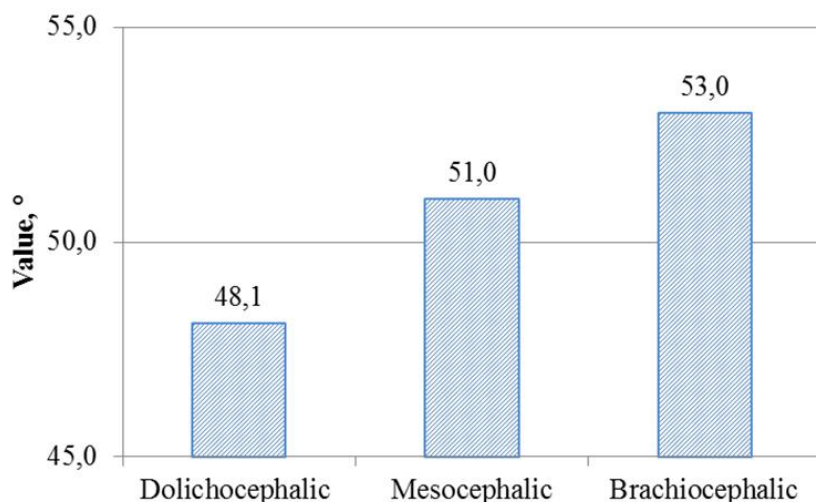


Fig. 4. Values of angle between medial and lateral walls in groups by a cranial index

Correlation coefficients between morphometric indicators of an orbit in groups by types of cranium are presented in tab. 3. Average degree correlation is observed only between orbital breadth and lengths of medial wall and orbital floor; orbital depth and lengths

of the orbital floor and roof; between lengths of the orbital floor and roof – at brachiocephals, and also between lengths of the orbital floor and roof – at dolichocephals and mesocephals. Correlations between the rests of the indicators combinations are absent.

Table 3
Correlation coefficients between morphometric indicators of an orbit in groups by types of cranium *

Indices	Type of cranium	Medial wall length, mm	Lateral wall length, mm	Orbital floor length, mm	Orbital roof length, mm	Orbital breadth, mm	Orbital height, mm	Orbital depth, mm	Angle of orbital entrance inclination, °	Angle between medial and lateral walls, °
Medial wall length, mm	D	1,00								
	M	1,00								
	B	1,00								
Lateral wall length, mm	D	0,23	1,00							
	M	0,26	1,00							
	B	0,44	1,00							
Orbital floor length, mm	D	0,48	0,22	1,00						
	M	0,24	0,25	1,00						
	B	0,47	0,17	1,00						
Orbital roof length, mm	D	0,39	0,57	0,79	1,00					
	M	-0,09	0,28	0,49	1,00					
	B	0,31	0,33	0,57	1,00					
Orbital breadth, mm	D	-0,48	0,34	-0,48	-0,14	1,00				
	M	0,43	0,22	0,31	0,23	1,00				
	B	0,52	0,13	0,51	0,31	1,00				
Orbital height, mm	D	-0,32	-0,66	-0,05	-0,09	-0,32	1,00			
	M	-0,09	0,23	0,19	0,26	0,08	1,00			
	B	0,08	-0,02	-0,08	-0,04	0,16	1,00			
Orbital depth, mm	D	0,31	-0,21	-0,32	-0,38	-0,32	0,10	1,00		
	M	0,39	-0,41	-0,13	-0,38	0,05	-0,19	1,00		
	B	0,40	0,32	0,52	0,59	0,38	0,01	1,00		
Angle of orbital entrance inclination, °	D	0,54	0,21	0,67	0,53	-0,68	0,10	0,35	1,00	
	M	0,08	0,27	-0,05	0,25	0,02	0,35	-0,39	1,00	
	B	0,11	0,05	0,04	0,13	0,14	0,13	0,14	1,00	
Angle between medial and lateral walls, °	D	-0,61	-0,08	-0,35	-0,08	0,29	0,28	-0,40	-0,39	1,00
	M	-0,29	0,24	-0,02	0,38	0,48	0,07	-0,24	-0,13	1,00
	B	-0,32	-0,21	-0,19	-0,01	-0,23	0,16	-0,38	-0,12	1,00

* - table cells with gray color show coefficients of correlation which reliable ($p \leq 0,05$) differ from zero

In the literature the number of publications and analyzed orbital morphometric indicators especially as regards types of cranium is limited. All of them relate exclusively to the linear indicators. Our data on orbital height and breadth in groups by types of cranium are consistent with [3] and are below than mentioned in [2]. As for other linear indicators they were studied only in [4], and out of connection with types of cranium. Correlation between morphometric indicators are not covered in references.

During planning reconstructive surgery at orbital bone structures differences between types of cranium in orbital height and breadth, lengths of lateral wall, orbital roof and floor and values of angle between medial and lateral walls should be considered.

CONCLUSIONS

1. Brachiocephals constitute 63 %, dolichocephals – 27 % and mesocephals – 10 % of the frequency distribution of the investigated population.

2. In groups by types of cranium length of medial wall reliable decreases from dolichocephalic persons to brachiocephalic; length of lateral wall, orbital roof and floor as well as orbital breadth – from mesocephalic persons to brachiocephalic. There are no reliable distinctions between types of cranium

in orbital height. The angle between medial and lateral walls of orbit reliable increases from dolichocephals to brachiocephals. The interrelation of changes of an angle of orbital entrance inclination and types of cranium is not observed.

3. The number of statistically significant correlations between morphometric indicators of an orbit increases from dolichocephals to brachiocephals at the absence of a reliable difference between them. Average degree correlation is noted only between orbital breadth and lengths of medial wall and orbital floor; orbital depth and lengths of the orbital floor and roof; between lengths of the orbital floor and roof – at brachiocephals, and also between lengths of the orbital floor and roof – at dolichocephals and mesocephals.

4. During planning reconstructive surgery at orbital bone structures differences between types of cranium in orbital height and breadth, lengths of lateral wall, orbital roof and floor and values of angle between medial and lateral walls should be considered.

PROSPECTS FOR FUTURE STUDIES

Deepening of ideas of quantitative anatomic norm of orbital bone structures by analysis of combinations of a sex, age and type of cranium factors is promising.

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OUTCOMES OF ARTERIAL HYPERTENSION IN PATIENTS WITH DIFFERENT TYPES OF SYSTOLIC BLOOD PRESSURE ORTHOSTATIC REACTIONS

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Peculiarities of currency and outcomes in arterial hypertension (AH) patients with hypotensive, isotensive and hypertensive orthostatic reactions (OR) of systolic arterial blood pressure (SBP) were studied in the follow up of 113 AH patients, age $64,73 \pm 6,42$ years (44 males and 69 females). According to the SBP in orthostatic test patients were divided into 3 groups: group 1 – hypotensive OR, group 2 – isotensive OR and group 3 – hypertensive OR. AH grades and stages frequencies, HF functional class after 4 years of treatment, and the severity and frequency of adverse cardiovascular events and outcomes were identified. Data was processed by the variation statistics methods. It was found that the less severe currency of AH is seen in hypertensive type, more severe in hypotensive type, and the most severe in isotensive type of SBP orthostatic reactions. In general quantity of adverse events and outcomes is more frequently seen in isotensive type of SBP OR – 46 %, is less frequently seen in hypertensive type – 18 %. In AH patients it is necessary to pay special attention not only to the BP control, but also to the optimization of SBP orthostatic reactions.

KEY WORDS: systolic blood pressure, orthostatic reactions, arterial hypertension

НАСЛІДКИ АРТЕРІАЛЬНОЇ ГІПЕРТЕНЗІЇ У ПАЦІЄНТІВ З РІЗНИМИ ТИПАМИ ОРТОСТАТИЧНИХ РЕАКЦІЙ СИСТОЛІЧНОГО АРТЕРІАЛЬНОГО ТИСКУ

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Вивчено особливості перебігу та наслідки артеріальної гіпертензії (АГ) у пацієнтів із гіпотензивними, ізотензивними і гіпертензивними ортостатичними реакціями (ОР) систолічного артеріального тиску (САТ) за результатами спостереження за 113 пацієнтами з АГ у віці $64,73 \pm 6,42$ років (44 чоловіка і 69 жінок). По змінам САТ в ортостатичній пробі пацієнти поділені на 3 групи: група 1 - гіпотензивна ОР, група 2 - ізотензивна ОР і група 3 - гіпертензивна ОР. Визначали частоти ступеня та стадії АГ, функціонального класу СН через 4 роки від початку лікування, а також ступінь та частоту несприятливих серцево-судинних випадків. Дані оброблені методами варіаційної статистики. Встановлено, що більш сприятливий перебіг АГ спостерігається при гіпертензивних і менш сприятливий при гіпотензивних типах ортостатичних реакцій САТ, несприятливий - при ізотензивном. Загальна кількість несприятливих результатів переважає при ізотензивном типі ОР САТ – 46 %, найменша їхня кількість при гіпертензивних – 18 %. У пацієнтів з АГ необхідно приділяти увагу не тільки контролю артеріального тиску, а й оптимізації ортостатичних реакцій САТ.

КЛЮЧОВІ СЛОВА: систолічний артеріальний тиск, ортостатичні реакції, артеріальна гіпертензія

ИСХОДЫ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ У ПАЦИЕНТОВ С РАЗНЫМИ ТИПАМИ ОРТОСТАТИЧЕСКИХ РЕАКЦИЙ СИСТОЛИЧЕСКОГО АРТЕРИАЛЬНОГО ДАВЛЕНИЯ

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Изучены особенности течения и исходы артериальной гипертензии (АГ) у пациентов с гипотензивными, изотензивными и гипертензивными ортостатическими реакциями (ОР) систолического артериального давления (САД) по результатам наблюдения за 113 пациентами с АГ в возрасте $64,73 \pm 6,42$ лет (44 мужчины и 69 женщин). По изменениям САД в ортостатической пробе пациенты разделены на 3 группы: группа 1 – гипотензивная ОР, группа 2 - изотензивная ОР и группа 3 – гипертензивная ОР. Определяли частоту степени и стадии АГ, функционального класса СН спустя 4 года от начала лечения, а также степень и частоту неблагоприятных сердечно-сосудистых исходов. Данные обработаны методами вариационной статистики. Установлено, что более благоприятное

течение АГ наблюдается при гипертензивном и менее благоприятное при гипотензивном типах ортостатических реакций САД, неблагоприятное - при изотензивном. Общее число неблагоприятных исходов преобладает при изотензивном типе ОР САД – 46 %, наименьшее их количество при гипертензивном – 18 %. У пациентов с АГ необходимо уделять внимание не только контролю АД, но и оптимизации ортостатических реакций САД.

КЛЮЧЕВЫЕ СЛОВА: систолическое артериальное давление, ортостатические реакции, артериальная гипертензия

INTRODUCTION

The problem of systolic blood pressure (SBP) orthostatic reactions (OR) clinical significance in patients with arterial hypertension (AH) is not thoroughly studied.

There are three main types of SBP OR (increase, no changes, decrease) [1, 2, 3, 4, 5], but the literature is mainly focused on hypotensive SBP OR, which is considered to be a cardiovascular mortality predictor [2, 3, 6].

Mentioned just above prompted us to perform the following study.

Study was performed as part of scientific-research work «Studies of nonlinear dynamic effects in autonomic regulation of cardiac biomechanics» № state registration 0103U004222 MoH of Ukraine.

OBJECTIVE

The aim of research - to study the peculiarities of AH course in patients with different types of SBP OR.

MATERIALS AND METHODS

A retrospective cohort study with 133 AH patients (age $64,73 \pm 6,42$ years, 44 males, 69 females) was done at polyclinics #6 of Moscow rayon of Kharkov. Average duration of disease was $13,9 \pm 6, 2$ years. Study excluded patients with myocardial infarction, acute stroke, heart failure IV functional class (fc), obesity degree III-IV, secondary hypertension.

Degree and stage of AH, heart failure (HF) functional class, were evaluated before the study and after 4 years of follow up. Also such outcomes as death, stroke, acute myocardial infarction were assessed by the end of the study.

Blood pressure was measured with Korotkov's method, tonometer Microlife BP AG1-20 in clinostasis after 5 minutes rest and in 3 minutes after entering orthostasis in the morning, fasting. Coffee, alcohol, medications

were limited for 24 hours, and physical activity for 30 minutes before the test.

Patients follow up started in 2004, all were given standard recommendations for lifestyle modification and diet, motivated for long-term use of drugs according to Ukrainian Society of Cardiologists recommendations [7]. Patients received β -blockers, angiotensin converting enzyme (ACE) inhibitors, calcium antagonists (CA). When insufficient BP control a diuretic (hydrochlorothiazide) was added. Patients voluntarily stopped taking medications were excluded from the study.

Prior to treatment, all patients were divided into 3 groups according to SBP OR. Group 1, hypotensive SBP OR (SBP decrease for more than 5 mmHg) included 20 patients (15 % of sample). Group 2, isotensive SBP OR (SBP changes ranged -5/+5 mmHg), included 31 patient (23 % of sample). Group 3, hypertensive SBP OR (SBP increase for more than 5 mmHg), included 82 patients (62 % of sample).

Frequencies of AH stages and degrees, HF functional classes were assessed in these groups during the study. Frequencies of cardiovascular outcomes were evaluated at the end of the study.

For the statistical evaluation of the results - parametric criteria were used (mean -M, standard deviation -sd). The significance of differences between groups was determined with Pearson criteria, calculations done using SPSS 10.0 for Windows.

RESULTS AND DISCUSSION

Table shows the ratio of basic clinical syndromes in AH patients with hypo-, iso- and hypertensive SBP OR types before and 4 after therapy start. Patients' redistribution towards disease progression was observed in all types of SBP OR. More intensive AH progression was seen in patients with isotensive SBP OR type. E.g., the frequency of severe AH in hypertensive type of SBP OR increased by 12 %, in hypotensive by 16 %, while in

isotensive type it increased by 23 %. The frequency of AH stage III in hypertensive SBP OR increased by 4 %, in hypotensive type by

10% and in isotensive by 13 %. HF II and III functional class frequency increase appeared at the same level in all three types of SBP OR.

Table

Frequency of major clinical syndromes in AH patients with different types of SBP OR before and in 4 years after the treatment start (n, %)

Index		Type of SBP OR					
		Hypotensive		Isotensive		Hypertensive	
		2004	2008	2004	2008	2004	2008
degree	Mild AH	2 (10)	1 (5)	19 (59)	7 (22)	57 (67)	30 (36)
	Moder AH	15 (71)	12 (60)	8 (25)	12 (39)	13 (15)	28 (34)
	Severe AH	4 (19)	7 (35)	5 (16)	12 (39)	15 (18)	24 (30)
stage	I	1 (5)	0	2 (7)	1 (4)	2 (3)	0
	II	18 (85)	16 (80)	27 (84)	23 (74)	76 (89)	72 (88)
	III	2 (10)	4 (20)	3 (9)	7 (22)	7 (8)	10 (12)
HF	I FC	8 (38)	4 (20)	6 (19)	3 (10)	22 (26)	15 (18)
	II FC	12 (57)	9 (45)	17 (53)	19 (61)	43 (51)	48 (58)
	III FC	1 (5)	4 (20)	3 (9)	6 (19)	6 (7)	14 (17)

Figure shows the frequency of cardiovascular endpoints in AH patients with hypo-, iso- and hypertensive types of SBP OR in 4 years after treatment start. The total number of adverse outcomes prevails at isotensive SBP OR type. In hypertensive SBP OR type it – 18 %, in hypotensive – 20 % and in isotensive – 46 %. Of those, the death rate in the hypertensive SBP OR type was lower if compared with hypo- and isotensive SBP OR

types (2 %, 5 % and 10 % respectively). Myocardial Infarction frequency in hypertensive SBP OR type was also lower than in isotensive SBP OR type (9 % and 23 % respectively) but was also higher than in hypotensive type (5 %). As for the stroke, its frequency in hypertensive SBP OR type was 3 % lower than that for hypotensive SBP OR type and 6 % lower than in isotensive SBP OR type.

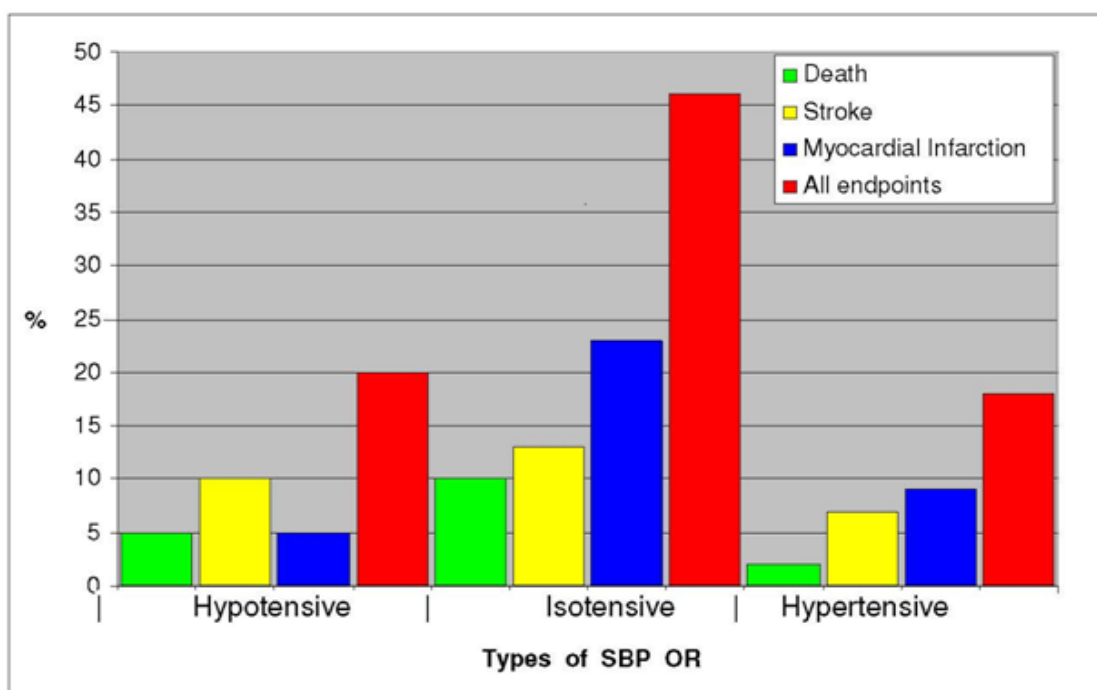


Fig. Frequency of adverse outcomes in AH patients with different types of SBP OR in 4 years after treatment start

In the issue of AH current with regards of SBP OR the attention is paid mainly to hypotensive SBP OR type [6, 8, 9, 10], whereas hypertensive and isotensive SBP OR types are almost not studied, while from physiological response to orthostasis point of view mentioned reactions can be also meaningful [11, 12]. As suggested by [9], hypertensive SBP OR type in elderly AH patients is a risk factor of «silent» strokes.

Obtained data demonstrates that SBP OR has an important role in AH long currency and outcomes. More severe currency and higher likelihood of adverse outcomes were observed in patients with isotensive SBP OR type when compared to hypo- and hypertensive SBP OR types.

Therefore, in AH patients, it is reasonable to pay attention not only to BP control, but also to take into account the SBP ORs.

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CONCLUSIONS

1. SBP OR type is important in AH clinical course and outcomes.
2. More favorable course and outcomes of AH are seen in hypertensive, less favorable in hypotensive, and adverse in isotensive SBP OR type.
3. AH patients' management should control not only the BP figures, but also SBP OR type.

PROSPECTS FOR FUTURE STUDIES

AH course and outcomes study in patients with different diastolic blood pressure (DBP) OR types can be reasonable.

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QTC INTERVAL DURATION CLASS AND STIMULATION PARAMETERS IN PATIENCE DURING FIRST SIX MONTHS AFTER PACEMAKER

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97 patients (55 men and 42 women) with implanted pacemakers (PM) in DDD/DDDR, VVI/VVIR and CRT modes were investigated. Pacing mode, location of the right ventricular (RV) and left ventricular (LV) electrode, percentage of the right atrium (RA), RV and LV stimulation, percentage of atrial flutter (AFI) and atrial fibrillation (AF), percentage of ventricular tachycardia (VT), base frequency of stimulation, RV and LV electrode impedance, RV and LV electrode stimulus amplitude and duration, RV electrode sensitivity, R-waves sensing, stimulated and detected AV-delay, interventricular delay, the minimum refractory period were evaluated in acute postoperative period (3-5 days) and six months after pacemaker implantation. Patients were divided into classes 1 (normal QTc (320-440 ms)) - 41 (42 %) of the patients) and class 2 (long QTc (> 440 ms)) - 56 (58 %) patients) of QTc interval duration. For data processing were used standard statistical procedures by Microsoft Excel. QTc interval prolongation is most often observed in patients with VVI/VVIR stimulation, normal QTc interval duration – in patients with CRT. The same part of normal and extended QTc interval duration is observed in patients with DDD/DDDR stimulation. Prolonged QTc interval duration is associated with more frequent RV electrode implantation in heart apex, higher percentage of AFI and AF, LV electrode impedance, RV and LV electrodes stimulus amplitude, detected and stimulated AV-delays, minimum refractory period in first six months after PM implantation. Patients with increased QTc interval duration after PM implantation require more intensive monitoring of stimulation parameters and enhancing medication.

KEY WORDS: cardiac pacing, stimulation parameters, electrocardiography, QTc interval

КЛАС ТРИВАЛОСТІ ІНТЕРВАЛУ QTC ТА ПАРАМЕТРИ СТИМУЛЯЦІЇ У ПАЦІЄНТІВ В ПЕРШІ ПІВРОКУ ПІСЛЯ ІМПЛАНТАЦІЇ ЕКС

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Обстежено 97 пацієнтів (55 чоловіків і 42 жінки) з імплантованими електрокардіостимуляторами (ЕКС) в режимах DDD/DDDR, VVI/VVIR і CRT. Оцінювали в гострому післяопераційному періоді (3-5 добу) і через півроку після імплантації ЕКС режим стимуляції, розташування правошлуночкового (ПШ) і лівошлуночкового (ЛШ) електрода, відсоток стимуляції правого передсердя (ПП), ПШ і ЛШ, відсоток тріпотіння передсердь (ТП) і фібриляції передсердь (ФП), відсоток шлуночкової тахікардії (ШТ), базова частота стимуляції, імпеданс ПШ і ЛШ електрода, амплітуда і тривалість стимулу ПШ і ЛШ електрода, чутливість ПШ електрода, сенсінг R-хвилі, стимульована і детектована AV-затримка, міжшлуночкова затримка, мінімальний рефрактерний період. Пацієнти були розділені на класи 1 (нормальної QTc (320-440 мс)) - 41 (42 %) пацієнтів) і 2 (подовженої QTc (> 440 мс)) - 56 (58 %) пацієнтів) тривалості інтервалу QTc. Для обробки даних використовувалися стандартні статистичні процедури за допомогою Microsoft Excel. Подовження тривалості інтервалу QTc найбільш часто спостерігалось у пацієнтів з VVI/VVIR ЕКС, нормальна тривалість інтервалу QTc - у пацієнтів з CRT. Однакова частота нормальної і подовженою тривалості інтервалу QTc спостерігалась у пацієнтів з DDD/DDDR ЕКС. Збільшення тривалості інтервалу QTc пов'язано з більш частою імплантацією ПШ електрода в верхівку серця, більшим відсотком ТП і ФП, імпедансом ЛШ електрода, амплітудою ПШ і ЛШ електродів, детектованою і стимульованою AV-затримками, мінімальним рефрактерним періодом в перші шість місяців після імплантації ЕКС. Пацієнти зі збільшенням тривалості інтервалу QTc після імплантації ЕКС вимагають більш інтенсивного моніторингу параметрів стимуляції та посилення медикаментозної терапії.

КЛЮЧОВІ СЛОВА: електрокардіостимуляція, параметри стимуляції, електрокардіографія, інтервал QTc

КЛАСС ПРОДОЛЖИТЕЛЬНОСТИ ИНТЕРВАЛА QTc И ПАРАМЕТРЫ СТИМУЛЯЦИИ У ПАЦИЕНТОВ В ПЕРВЫЕ ПОЛГОДА ПОСЛЕ ИМПЛАНТАЦИИ ЭКС

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Обследованы 97 пациентов (55 мужчин и 42 женщины) с имплантированными электрокардиостимуляторами (ЭКС) в режимах DDD/DDDR, VVI/VVIR и CRT. Оценивали в остром послеоперационном периоде (3-5 сутки) и через полгода после имплантации ЭКС режим стимуляции, расположение правожелудочкового (ПЖ) и левожелудочкового (ЛЖ) электрода, процент стимуляции правого предсердия (ПП), ПЖ и ЛЖ, процент трепетания предсердий (ТП) и фибрилляции предсердий (ФП), процент желудочковой тахикардии (ЖТ), базовая частота стимуляции, импеданс ПЖ и ЛЖ электрода, амплитуда и длительность стимула ПЖ и ЛЖ электрода, чувствительность ПЖ электрода, сенсинг R-волны, стимулированная и детектированная AV-задержка, межжелудочковая задержка, минимальный рефрактерный период. Пациенты были разделены на классы 1 (нормальной QTc (320-440 мс)) - 41 (42 %) пациентов) и 2 (удлиненной QTc (> 440 мс)) – 56 (58 %) пациентов) продолжительности интервала QTc. Для обработки данных использовались стандартные статистические процедуры с помощью Microsoft Excel. Удлинение продолжительности интервала QTc наиболее часто наблюдалось у пациентов с VVI/VVIR ЭКС, нормальная продолжительность интервала QTc – у пациентов с CRT. Одинаковая частота нормальной и удлиненной продолжительности интервала QTc наблюдалась у пациентов с DDD/DDDR ЭКС. Увеличение продолжительности интервала QTc связано с более частой имплантацией ПЖ электрода в верхушку сердца, большим процентом ТП и ФП, импедансом ЛЖ электрода, амплитудой ПЖ и ЛЖ электродов, детектированными и стимулированными AV-задержками, минимальным рефрактерным периодом в первые шесть месяцев после имплантации ЭКС. Пациенты с увеличением продолжительности интервала QTc после имплантации ЭКС требуют более интенсивного мониторинга параметров стимуляции и усиления медикаментозной терапии.

КЛЮЧЕВЫЕ СЛОВА: электрокардиостимуляция, параметры стимуляции, электрокардиография, интервал QTc

INTRODUCTION

Cardiac pacing is one of the leading treatment methods for bradyarrhythmias and chronic heart failure (CHF) [1]. Stimulation parameters monitoring and correction allows control the paced rhythm and accompanying medical treatment [1-3].

Output of corrected QT interval duration (QTc) values beyond physiological scope is a poor prognostic sign, not only in patients with spontaneous rhythm, but also with the pacemaker (PM) [4, 5]. Despite this, stimulation parameters in QTc interval duration classes in patients with PM have not previously been studied.

OBJECTIVE

The purpose of the study is to estimate stimulation parameters in patients during first six months after pacemaker implantation in different modes in QTc interval duration classes.

MATERIALS AND METHODS

97 patients aged 68 ± 10 (M \pm sd) (55 – female, 42 – male) were examined in the

department of ultrasound and instrumental diagnostics with miniinvasive interventions of GI «Zaycev V.T. Institute of General and Urgent Surgery of NAMS of Ukraine», among them – 21 patients have atrial fibrillation (AF). All patients were underwent permanent pacing therapy from 2006 to 2013 in modes: DDD (17 patients), DDR (28 patients), VVI (22 patients), VVIR (12 patients) and CRT (18 patients). RV pacing more than 50 % was observed in 35 (78 %) patients. Mainly atrial pacing (AP) (90 %) during DDD/DDDR pacing was observed in 8 patients (18 %) with sick sinus node syndrome (SSNS).

Patients aged less than 40 years, with concomitant stable angina III-IV functional class (FC), a single-chamber atrial pacing and dual chamber atrioventricular pacing with right ventricle (RV) stimulation less than 50 % were excluded from the study.

Pacing mode, location of the RV and left ventricular (LV) electrode, percentage of the right atrium (RA), RV and LV stimulation, percentage of atrial flutter (AFL) and atrial fibrillation (AF), percentage of ventricular tachycardia (VT), base frequency of stimulation, RV and LV electrode impedance,

RV and LV electrode stimulus amplitude and duration, RV electrode sensitivity, R-waves sensing, stimulated and detected AV-delay, interventricular delay, the minimum refractory period were evaluated in acute postoperative period (3-5 hours) and six months after.

To measure the duration of the QT interval and heart rate of the patients before and after pacemaker implantation (3-5 days after surgery) were recorded on a computer ECG electrocardiograph «Cardiolab +» (HAI-Medica). The stimulated QTc interval duration was measured after the removal of the stimulus artifact in three consecutive complexes of the Q wave to the beginning of the descending segment of the return of the T wave in leads to the contour II, V5, and V6 with choosing of a maximum value. The corrected QT interval duration (QTc) of the patients with spontaneous rhythm and pacing was calculated by the Bazett formula: $QTc = QT / (RR \wedge 0,5)$. For patients with AF, QTc was calculated using the formula $QTc = QT + 0,154 \times (1000 - RR)$ Fremingem study for patients with atrial fibrillation [6], the measurement accuracy - 0.5 ms.

The patients with pacemakers were divided into 3 classes of QTc interval duration of stimulated complexes (further classes): Class 1 - normal (in the physiological range of values

- 320-439 ms, Class 2 - (qualified) an elongated QTc interval- > 440 ms, and Class 3 - (qualified) shortened QTc interval - < 320 ms [7].

There are a 41 (42 %) patients aged 66 ± 10 in class 1 (male - 20 female - 21) and 56 (58 %) patients aged 69 ± 9 in class 2 (male - 35 female - 21). In class 3, there was not a single patient. Values were estimated in QTc interval duration classes in acute postoperative period (3-5 hours) and six months after.

The data were processed after formation the Microsoft Excel and Statistica base. For statistical evaluation of the results, the parametric criteria (mean - M, standard deviation - sd) and nonparametric ones (absolute (n, number) and relative (percentage of (p, %) and the criterion χ^2) units) were used. The probability of differences between groups was determined using a non-parametric U - Mann-Whitney test. The expected result is determined by levels of reliability $p < 0.01$ and $p < 0.05$.

RESULTS AND DISCUSSION

The proportion of patients with a pacemaker in various stimulation modes in QTc interval duration classes is shown in Fig. 1.

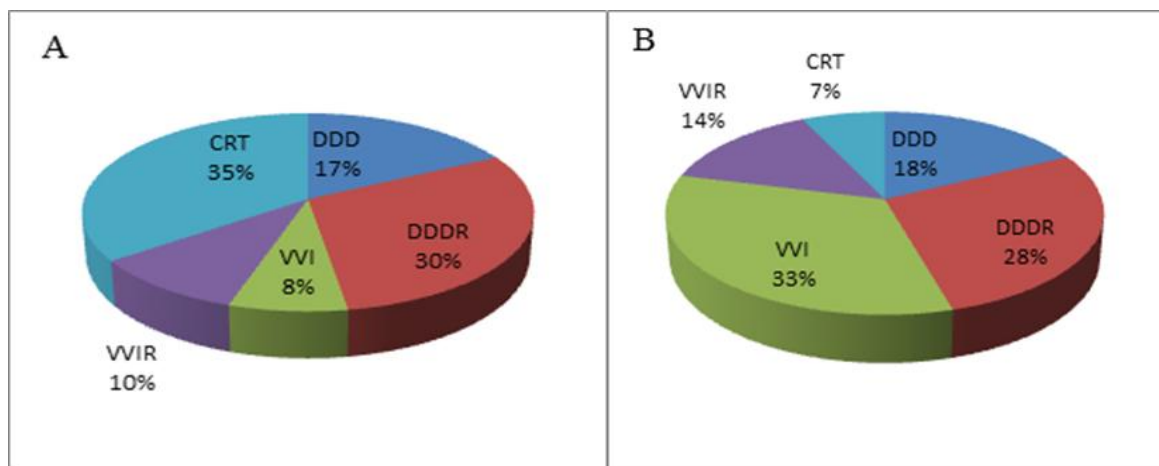


Fig. 1. Proportion of patients with a pacemaker in various stimulation modes: A - in the class 1 of QTc interval duration; B - in the class 2 of QTc interval duration.

The share of CRT in class 1 of QTc interval duration was five times greater than in class 2. Single-chamber VVI pacing mode more frequently observed in the class 2 of QTc interval duration, and much less in the class 1. The percentage of patients with DDD, DDDR,

VVIR pacemakers did not differ in both classes of QTc interval duration.

Stimulation parameters in patients during first six months after pacemaker implantation in QTc interval duration classes are presented in the table 1.

Table 1

Stimulation parameters in patients during first six months after pacemaker implantation in QTc interval duration classes

Stimulation parameters		QTc interval duration class			
		Class 1		Class 2	
		Acute postoperative period	After 6 months	Acute postoperative period	After 6 months
Location of RV electrode (%±p)	Apex	5 ± 3	-/-	12 ± 4*	-/-
	The upper third of IVS	29 ± 5*	-/-	17 ± 7	-/-
	The middle third of IVS	60 ± 6	-/-	56 ± 10	-/-
	The lower third of IVS	6 ± 3	-/-	15 ± 5*	-/-
Location of LV electrode (%±p)	Endocardial	17 ± 12	-/-	5 ± 4	-/-
	Epicardial	83 ± 12	-/-	95 ± 4	-/-
Percentage of stimulation (%±p)	RA	27 ± 12	32 ± 13	41 ± 9	44 ± 9
	RV	88 ± 14	76 ± 15	81 ± 7	90 ± 11
	LV	96 ± 4	97 ± 4	97 ± 5	98 ± 5
Percentage of AFI/AF (%±p)		1,6 ± 0,2	1,9 ± 0,5	2,0 ± 0,3*	3,4 ± 0,6* ^{**}
Percentage of VT (%±p)		-	0,1 ± 0,05	0,2 ± 0,05	0,3 ± 0,1
Base frequency of stimulation (M±sd, 1/min)		71 ± 9	69±8	62±3	66±5
Impedance (M±sd, Om)	RV electrode	588 ± 26	608±28	592±21	636±34
	LV electrode	206 ± 42	228±41	271±32*	338±29 ^{*,**}
Stimulus amplitude (M±sd, V)	RV electrode	0,4 ± 0,2	0,9±0,3 ^{**}	1,3±0,3*	2±0,4 ^{*,**}
	LV electrode	4,1 ± 0,4	3,7±0,4	5,1±0,8*	6±0,9*
Stimulus duration (M±sd, ms)	RV electrode	0,4 ± 0,1	0,4±0,1	0,4±0,1	0,4±0,2
	LV electrode	1,1 ± 0,1	1,2±0,1	1,5±0,2*	1,5±0,2
RV electrode sensitivity (M±sd, mV)		0,7 ± 0,2	0,8±0,2	1,2±0,4	0,9±0,3
R-wave sensing (M±sd, mV)		5,1 ± 1	6,7±0,5 ^{**}	6,2±1,1	8,1±2 ^{**}
Stimulated AV-delay (M±sd, ms)		134 ± 18	140±21	132±22	165±19 ^{*,**}
Detected AV-delay (M±sd, ms)		106 ± 9	112±10	118±10	130±21*
Interventricular delay (M±sd, ms)		42 ± 7	48±6	43±10	49±11
Min refractory period (M±sd, ms)		251 ± 12	276±15 ^{**}	306±24*	361±27 ^{*,**}

Notes: * p < 0,05 – between values in classes; ** p < 0,05 – between values in different stages after PM implantation.

RV electrode is more often located in upper and middle thirds of interventricular septum (IVS) in the class 1 and in lower third of IVS and heart apex in the class 2 of QTc interval duration (p < 0.05).

Percentage of RA, RV and LV stimulation in patients in classes 1 and 2 of QTc interval

duration in the acute postoperative period and six months after pacemaker implantation was the same.

Percentage of AFI and AF of all time of stimulation in acute postoperative period after pacemaker implantation was greater in the class 2 than in the class 1 of QTc interval

duration, six months after pacemaker implantation in class 1 it did not change, in the class 2 - increased ($p < 0,05$). The percentage of VT was similar in classes 1 and 2, the entire period of observation.

Base frequency of stimulation in both classes of the QTc interval duration at different stages after pacemaker implantation was the same.

RV electrode impedance did not differ in QTc interval duration classes both in acute postoperative period, and six months after pacemaker implantation. LV electrode impedance in acute postoperative period was higher in class 2 of QTc interval duration, in the semi-annual period of observation, it did not change in class 1 and increased in class 2 ($p < 0,05$). RV and LV electrodes stimulus amplitude in acute postoperative period was higher in class 2 of QTc interval duration, and six months after pacemaker implantation has increased only in class 2 for the RV electrode.

In classes 1 and 2 of QTc interval duration at different stages after pacemaker implantation stimulus duration of RV and LV electrodes, as well as the sensitivity of RV electrode did not differ.

R-wave sensing in QT interval duration classes was similar, increasing in equal measure to semi-annual period of observation after pacemaker implantation.

Detected and stimulated AV-delays in acute postoperative period after pacemaker implantation were similar in QTc interval duration classes, and six months after has increased only in class 2 ($p < 0,05$).

Interventricular delay was the same in classes 1 and 2 of QTc interval duration in acute postoperative period and six months after pacemaker implantation. Minimum refractory period in the acute postoperative period was higher in class 2 of QTc interval duration, to semi-annual period from it has increased, mostly in class 2.

More frequent CRT pacemaker implantation in patients with QTc interval prolongation in our study is consistent with the [8] and due to the fact that the extension of the complex QRS, like one of its parts, is an indication for CRT implantation. We have not been found data on relationship of QTc interval duration class with frequency of one- and dual-chamber devices implantation.

We, as well as [9], it was shown the connection of RV electrode implantation in

apex and QTc interval prolongation, but unlike [10], where it was shown also after RV electrode implantation in IVS, we had no a similar QTc interval prolongation. This is probably due to the greater proportion of patients in our research with position of the RV electrode in upper and middle thirds of IVS, where the conduction of excitation closest to the physiological.

Relationship of QTc interval prolongation and higher frequency of AFI and AF in patients with implanted pacemaker, was shown us, confirms the data [11].

Increased stimulated AV-delay in semi-annual period after pacemaker implantation in patients with baseline QTc interval duration prolongation, we received corresponds to [12], such a connection to the detected AV-delay were not previously investigated.

LV electrode location, percentage of RA, RV and LV stimulation, percentage of VT, base frequency of stimulation, impedance, amplitude and duration of RV and LV electrodes stimulus, RV electrode sensitivity, R-wave sensing, interventricular delay and minimum refractory period have not previously been studied in QTc interval duration classes.

Changes in stimulation parameters in patients during first six months after PM implantation are determined in generally, among other factors, by QTc interval duration class. There more often changes in patients with prolonged QTc interval duration indicate that they require more intensive PM monitoring and therapeutic management.

CONCLUSIONS

1. QTc interval prolongation is most often observed in patients with VVI/VVIR stimulation, normal QTc interval duration – in patients with CRT. The same part of normal and extended QTc interval duration is observed in patients with DDD/DDDR stimulation.

2. Prolonged QTc interval duration is associated with more frequent RV electrode implantation in heart apex, higher percentage of AFI and AF, LV electrode impedance, RV and LV electrodes stimulus amplitude, detected and stimulated AV-delays, minimum refractory period in first six months after PM implantation.

3. Patients with increased QTc interval duration after PM implantation require more intensive monitoring of stimulation parameters and enhancing medication.

PROSPECTS FOR FUTURE STUDIES

It seems appropriate to investigate the relationship between QTc interval duration after right ventricular PM implantation and

changes in stimulation parameters after correction of drug therapy in the class of prolonged QTc interval duration in late postoperative period.

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GENERAL CARDIOVASCULAR RISK AND THE CLINICAL CONDITION OF PATIENTS WITH ATRIAL FIBRILLATION

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General cardiovascular risk (GCVR) in the clinical condition of patients with atrial fibrillation (AF) on 282 patients (165 men and 117 women) aged $64,6 \pm 9,7$ years was studied. In 137 patients was diagnosed permanent AF and in 145 - persistent with duration of the disease from 3 months to 25 years. Sex and age of the patients, form and duration of AF, functional class (FC) of IHD, presence of postinfarction cardiosclerosis, stage and severity of AH, stage and functional class (FC) of HF, class EHRA of AF was determined. GCVR was calculated in accordance with the scale SCORE. Patients were classified into groups of GCVR. Statistical evaluation was performed by parametric (estimation of mean (M) and standard deviation (sd)) and non-parametric (Student t-test and Mann-Whitney test) methods. Expediency of using GCVR in assessing severity of the health status of patients with AF was demonstrated. With the rise of GCVR class increases frequency and severity of arterial hypertension, IHD and HF. Patients with AF require for more attention with increasing of GCVR class.

KEY WORDS: general cardiovascular risk, atrial fibrillation, clinical condition

ЗАГАЛЬНИЙ КАРДІОВАСКУЛЯРНИЙ РИЗИК ТА КЛІНІЧНИЙ СТАН ПАЦІЄНТІВ З ФІБРИЛЯЦІЄЮ ПЕРЕДСЕРДЬ

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Вивчено загальний кардіоваскулярний ризик (ЗКВР) у клінічному стані пацієнтів з фібриляцією передсердь на 282 пацієнтах (165 чоловіків та 117 жінок) у віці $64,6 \pm 9,7$ років. У 137 діагностована постійна і у 145 персистуюча ФП давністю від 3 місяців до 25 років. Визначали стать і вік пацієнтів, форму та давність ФП, функціональний клас (ФК) ІХС, наявність післяінфарктного кардіосклерозу, стадію і ступінь тяжкості АГ, стадію і функціональний клас (ФК) СН. ЗКВР розраховували в відповідності до шкали SCORE. Пацієнтів класифікували на групи ЗКВР. Статистична обробка результатів проводилась параметричними з визначенням середнього значення (М) та стандартного відхилення (sd) і непараметричними t-критерієм Стьюдента та критерієм Манна-Уїтні методами. Показана доцільність використання ЗКВР у оцінці тяжкості стану здоров'я пацієнтів з ФП. Зі збільшенням класу ЗКВР збільшуються частота та підвищуються тяжкість АГ, ІХС та СН. Пацієнти з ФП потребують тим більше уваги, чим вищий клас ЗКВР.

КЛЮЧОВІ СЛОВА: загальний кардіоваскулярний ризик, фібриляція передсердь, клінічний стан

ОБЩИЙ КАРДИОВАСКУЛЯРНЫЙ РИСК И КЛИНИЧЕСКОЕ СОСТОЯНИЕ ПАЦИЕНТОВ С ФИБРИЛЛЯЦИЕЙ ПРЕДСЕРДИЙ

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Изучен общий кардиоваскулярный риск (ОКВР) в клиническом состоянии пациентов с фибрилляцией предсердий (ФП) на 282 пациентах (165 мужчин и 117 женщин) в возрасте $64,6 \pm 9,7$ лет. У 137 диагностирована постоянная и у 145 персистирующая ФП давностью от 3 месяцев до 25 лет. Определяли пол и возраст пациентов, форму и давность ФП, функциональный класс (ФК) ИБС, наличие постинфарктного кардиосклероза, стадию и степень тяжести АГ, стадию и функциональный класс (ФК) СН, класс EHRA ФП. ОКВР рассчитывали в соответствии со шкалой SCORE. Пациентов классифицировали на группы ОКВР. Статистическая оценка результатов проводилась параметрическими с оценкой среднего (М) и стандартного отклонения (sd) и непараметрическими t-критерием Стьюдента и критерием Манна-Уитни методами. Показана целесообразность

использования ОКВР в оценке тяжести состояния здоровья пациентов с ФП. С повышением класса ОКВР повышается частота и возрастает тяжесть артериальной гипертензии, ИБС и СН. Пациенты с ФП требуют тем большего внимания, чем больше класс ОКВР.

КЛЮЧЕВЫЕ СЛОВА: общий кардиоваскулярный риск, фибрилляция предсердий, клиническое состояние

INTRODUCTION

Atrial fibrillation (AF) is a serious medical and social problem as one of the leading causes of development and progression of heart failure (HF), thromboembolic complications, especially stroke, deterioration of life quality and expectancy in patients with significant increasing of treatment cost [1-5].

In assessing the state of patients' health and prediction of AF's outcome, evaluation of general cardiovascular risk (GCVR) on SCORE scale, proposed for estimation of risk of fatal cardiovascular diseases during 10 years, can be prospective. However, we have not found such research.

OBJECTIVE

The purpose of the study is to assess the value of general cardiovascular risk in the clinical condition of patients with atrial fibrillation.

MATERIALS AND METHODS

On the base of cardiology department of the central clinical hospital «Ukrzaliznytsia» and the city polyclinic №6 282 patients (165 men and 117 women) aged $64,6 \pm 9,7$ years were examined. In 137 patients was diagnosed permanent AF and in 145 - persistent with duration of the disease from 3 months to 25 years. Arterial hypertension (AH) was diagnosed in 235 patients, ischemic heart disease (IHD) - in 139 patients, postinfarction cardiosclerosis (PICS) - in 34 patients, heart failure (HF) - in 248 patients.

Exclusion criteria from the study were stable angina IV functional class (FC), acute coronary syndrome, heart failure IV FC and valvular heart disease.

Sex and age of the patients, form and duration of AF, functional class (FC) of IHD, presence of postinfarction cardiosclerosis, stage and severity of AH, stage and functional class (FC) of HF, class EHRA of AF was determined.

GCVR was calculated in accordance with the scale SCORE.

All patients were classified into 4 groups of GCVR: I - low (risk SCORE <1 %); II - moderate (risk SCORE $>1\%$ and <5 %); III - high (risk SCORE >5 % and <10 %) and IV - very high (SCORE >10 %) risk.

The data were entered into the database Microsoft Excel 2010. Statistical evaluation was performed by parametric (estimation of mean (M) and standard deviation (sd)) and non-parametric (Student t-test and Mann-Whitney test) methods.

RESULTS AND DISCUSSION

In table presents our findings about changes of the frequency of main clinical symptoms' occurrence in patients with AF depending on severity of GCVR.

The age of patients naturally increases with increasing of GCVR that explains its place among the classifying factors of GCVR.

In groups of low and moderate GCVR numbers of men and women were almost equally. In groups of high and very high risk male patients were dominated: 2 times in group of high and 1.5 times - in very high risk.

Depending on duration of AF groups of GCVR did not differ.

AH was diagnosed in 60 % of patients with low, in 72 % - with moderate, in 77 % - with high and in 90 % - with very high GCVR. II stage of AH was prevalent in all groups of GCVR. Frequency of III stage of AH was increased with GCVR from 0 % in the group with a low to 6 %, 18 % and 29 % with moderate, high and very high risk.

IHD was absent in patients with low GCVR and observed in 4 %, 11 % and 78 %, respectively, with moderate, high and very high GCVR.

PICS was diagnosed in 44 % of patients with IHD in group of very high GCVR.

HF was diagnosed in 88% of patients. Majority was comprised by patients with II A stage in all groups from low to very high GCVR (respectively 57 %, 50 %, 43 % and 60 %). II FC of HF was also predominant in all groups and ranged from 43 % in patients with low to 59 % - with very high GCVR.

Table

Clinical characteristics of patients with AF in groups of GCVR (% , M ± sd)

Clinical characteristics		I – low (n – 10)	II – moderate (n – 67)	III –high (n – 35)	IV – very high (n – 170)
Age		48,1 ± 6,4	58,7 ± 6,8	66,3 ± 9,8	67,4 ± 8,8
sex	male	5	30	26	104
	female	5	37	9	66
AF	permanent	4	20	22	91
	persistent	6	47	13	79
Duration of AF, years		7,1 ± 7,4	5,3 ± 4,2	7,3 ± 5,9	6,7 ± 6,4
AH, stage	0	4	19	8	16
	I	1	1	2	4
	II	5	44	20	105
	III	0	3	5	45
AH, degree	1	1	8	3	20
	2	3	32	18	81
	3	2	8	6	53
IHD, FC	0	10	64	31	38
	I	0	0	1	32
	II	0	3	3	67
	III	0	0	0	33
PICS		0	0	0	34
HF, stage	0	3	13	7	11
	I	3	19	11	43
	II A	4	27	12	95
	II Б	-	8	5	21
HF, FC	I	2	16	5	18
	II	3	27	14	94
	III	2	11	9	47
AF, EHRA	I	6	32	7	17
	II	4	20	23	38
	III		15	15	115

Class I EHRA was diagnosed in 22 %, class II – 27 %, class III - in 51 % of patients. In low and moderate GCVR majority was comprised by patients with class I and II EHRA, in groups with high and very high GCVR risk class III EHRA was dominated.

Evaluation of GCVR with the procedure of its definition proposed by the European Society of Hypertension and the European Society of Cardiology in 2007 and refined in recommendations in 2013 [6]. Its use is recommended in patients with arterial hypertension, but common risk factors for the entire set of somatic heart diseases provide a basis of its application in patients with AF, the more that a significant part of them have the

comorbidity of arterial hypertension with AF [7-8].

This publication confirms this assumption. Moreover, taking into account the worsening of the clinical condition of patients with AF with increasing of GCVR, its definition should be the standard for patients' managing. Class of GCVR should be included in the diagnosis of AF and considered in treatment strategies, especially with regard to the so-called «therapy against the current» [9-10].

CONCLUSIONS

Fulfilled study shows the feasibility of using GCVR in assessing the severity of the health status of patients with AF.

The frequency and severity of arterial hypertension, IHD and HF increases with increasing of GCVR class.

Patients with AF require for more attention with increasing of GCVR class.

PROSPECTS FOR FUTURE STUDIES

It is interesting to evaluate functional indicators in patients with AF in different groups of GCVR and their dynamics during treatment.

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PACING PARAMETERS CHANGES IN PATIENTS WITH IMPLANTED PACEMAKER IN DIFFERENT QRS COMPLEX DURATION CLASSES AT THE ANNUAL OBSERVATION STAGE

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100 patients (46 – women, 54 – men) 69 ± 7 years old with implanted pacemaker in three QRS complex duration classes (under 120, 120-149, 150 and more ms) were investigated in the early postoperative period, six months and a year of permanent pacing. Basic pacing rate, atrioventricular (AV) delay (stimulated and detected), ventricular threshold, ventricular lead impedance, percentage of ventricular pacing, percentage of atrial fibrillation/flutter time were measured. Basic pacing rate, stimulated and detected AV-delay, as well as the percentage of ventricular pacing were not associated with QRS complex duration classes and had not been changed in observation stages. Ventricular threshold, ventricular lead impedance and the percentage of atrial fibrillation/atrial flutter time in the annual monitoring stage were defined to QRS complex duration class. Ventricular threshold in the first six months of observation was not changed in any QRS complex duration classes and grew at an annual stage in class 3. The impedance of the ventricular lead in the first six months decreased in all classes, it was stabled at the year in classes 2 and 3 and was continued to decline in the class 1. Percentage of atrial fibrillation/flutter time was initially higher in class 3, and was decreased in six month observation stage, however, without reaching the values in classes 1 and 2.

KEY WORDS: permanent pacing, QRS complex duration, pacing parameters

ЗМІНИ ПАРАМЕТРІВ ЕЛЕКТРОКАРДІОСТИМУЛЯЦІЇ У ПАЦІЄНТІВ З ІМПЛАНТОВАНИМИ ЕКС В РІЗНИХ КЛАСАХ ТРИВАЛОСТІ QRS КОМПЛЕКСУ НА РІЧНОМУ ЕТАПІ СПОСТЕРЕЖЕННЯ

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Обстежені 100 пацієнтів (46 – жінок, 54 – чоловіків) у віці 69±7 років з імплантованими ЕКС в трьох класах тривалості QRS комплексу (до 120, 120-149, 150 і більше мс) в ранній післяопераційний період, 6 місяців і рік постійної електрокардіостимуляції (ЕКС). Визначалися базова частота стимуляції, атріовентрикулярна затримка (стимульована і детектована), поріг стимуляції шлуночків, імпеданс шлуночкового електрода, відсоток шлуночкової стимуляції, відсоток часу фібриляції/тріпотіння передсердь (ФП/ТП). Базова частота, стимульована і детектована AV-затримка, а також відсоток шлуночкової стимуляції не були пов'язані з класами тривалості QRS комплексу і не змінювалися на етапах ЕКС. Поріг шлуночкової стимуляції, імпеданс шлуночкового електрода і відсоток часу ФП/ТП в річному етапі спостереження визначалися класами тривалості QRS комплексу. Поріг шлуночкової стимуляції в перші півроку спостереження не змінювався ні в одному з класів і зростав на річному етапі в класі 3. Імпеданс шлуночкового електрода в перші півроку зменшувався у всіх класах, стабілізувавшись до року в класах 2 і 3 і продовживши зменшуватися в класі 1. Відсоток часу ФП/ТП, спочатку більш високий в класі 3, до піврічного періоду зменшувався, не досягаючи, однак, значень у класах 1 і 2.

КЛЮЧОВІ СЛОВА: постійна електрокардіостимуляція, тривалість QRS комплексу, параметри електрокардіостимуляції

ИЗМЕНЕНИЯ ПАРАМЕТРОВ ЭЛЕКТРОКАРДИОСТИМУЛЯЦИИ У ПАЦИЕНТОВ С ИМПЛАНТИРОВАННЫМИ ЭКС В РАЗНЫХ КЛАССАХ ПРОДОЛЖИТЕЛЬНОСТИ QRS КОМПЛЕКСА НА ГОДИЧНОМ ЭТАПЕ НАБЛЮДЕНИЯ

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Обследованы 100 пациентов (46 – женщин, 54 – мужчин) в возрасте 69 ± 7 лет с имплантированными ЭКС в трех классах продолжительности QRS комплекса (до 120, 120-149, 150 и более мс) в ранний послеоперационный период, 6 месяцев и год постоянной электрокардиостимуляции (ЭКС). Определялись базовая частота стимуляции, атриовентрикулярная задержка (стимулированная и детектированная), порог стимуляции желудочков, импеданс желудочкового электрода, процент желудочковой стимуляции, процент времени фибрилляции/трепетания предсердий (ФП/ТП). Базовая частота, стимулированная и детектированная AV-задержка, а также процент желудочковой стимуляции не были связаны с классами продолжительности QRS комплекса и не изменялись на этапах ЭКС. Порог желудочковой стимуляции, импеданс желудочкового электрода и процент времени ФП/ТП в годичном этапе наблюдения определялись классами продолжительности QRS комплекса. Порог желудочковой стимуляции в первые полгода наблюдения не изменялся ни в одном из классов и возрастал на годовом этапе в классе 3. Импеданс желудочкового электрода в первые полгода уменьшался во всех классах, стабилизировавшись к году в классах 2 и 3 и продолжив уменьшаться в классе 1. Процент времени ФП/ТП, изначально более высокий в классе 3, к полугодовому периоду уменьшался, не достигая, однако, значений в классах 1 и 2.

КЛЮЧЕВЫЕ СЛОВА: постоянная электрокардиостимуляция, продолжительность QRS комплекса, параметры электрокардиостимуляции

INTRODUCTION

Pacing parameters are estimated and programmed if necessary during each visit of patient with permanent pacemaker [1, 2].

Moreover, there are evidences about the relationship of separate pacing parameters with QRS complex duration for example ventricular lead impedance and threshold [3], the changes of pacing parameters on annual observation stage have not previously been studied.

OBJECTIVE

Purpose of this study – to assess pacing parameters changes in different QRS complex duration classes at the annual observation stage in patients with implanted pacemakers.

MATERIALS AND METHODS

100 patients (46 – women, 54 – men) with implanted pacemaker were examined in the department of ultrasound and clinical-instrumental diagnosis and minimally invasive interventions SI «V.T. Zaytsev Institute of General and Emergency Surgery NAMS of Ukraine». Mean age of the patients was 69 ± 7 years. The indications for pacemaker implantation were the atrio-ventricular (AV) block far-advanced II and III degree. We used

the following pacemakers: SJM Verity ADx XL SR 5156 and VVI Medtronic Sensia SEDR01 DDD.

Patients received indications of angiotensin converting enzyme inhibitors (ACE inhibitors, in moderate doses of enalapril maleate – 10 mg ramipril – 5mg, fosinopril – 10 mg, lisinopril – 10 mg, perindopril – 2 mg, captopril – 12.5 mg), angiotensin receptor antagonists II (ARA II, losartan in high doses – 50 mg, candesartan – 8 mg), beta-blockers (average dose bisoprolol – 5mg, metoprolol – 100 mg, carvedilol – 6.25 mg, betaxolol – 5 mg, atenolol – 50 mg) amiodarone (average dose 200 mg), acetylsalicylic acid (ASA – 75 mg), oral anticoagulants (AC at moderate doses of warfarin – 5mg or dabigatran – 220 mg), statins (atorvastatin in high doses – 20 mg, rosuvastatin –20 mg), and diuretics (furosemide in high doses – 40 mg, torasemide – 5 mg, hydrochlorothiazide – 12.5 mg, indapamide – 2.5 mg, spironolactone – 50 mg).

Electrocardiogram (ECG) was performed on the computer electrocardiograph Cardiolab + 2000. QRS complex duration was measured in leads II, V5, V6 (the average value of three consecutive complexes) with a choice of maximum value. Accuracy of measurement of QRS complex duration – 1 ms.

The pacemaker programmer defines the basic pacing rate, atrioventricular delay (stimulated and detected), the threshold of ventricular pacing, ventricular lead impedance, the percentage of ventricular pacing, the percentage of time atrial fibrillation/flutter.

Patients were assigned to three QRS complex duration classes according with Haghjoo M. et al: 1 – 120 ms (normal), 2 – 120-149 ms (long) and the 150 ms or more (substantially elongate). The above parameters were evaluated in selected classes in the early postoperative period (third to fifth day after pacemaker implantation), after 6 months and annual observation stage.

The data were brought into the Microsoft Excel base. For statistical evaluation of the results were used the parametric criteria (the mean – M, the standard deviation – sd). Comparing of QRS duration complex classes on the observation stages was conducted on each separate functional blood circulation value using a non-parametric U-Mann-Whitney test. Probable results were determined at levels of reliability $p < 0.05$.

RESULTS AND DISCUSSION

Table 1 shows the pacing parameters in patients in different QRS complex duration classes at the annual observation stage.

Table 1

Pacing parameters in patients in different QRS complex duration classes at the annual observation stage

Pacing parameters, (M±sd)	QRS complex duration									
	Under 120 ms			120-149 ms			150 and more ms			
	Early postoperative period	6 months later	Year later	Early postoperative period	6 months later	Year later	Early postoperative period	6 months later	Year later	
Basic pacing rate, 1/min	68 ± 6	65 ± 3	63 ± 6	70 ± 10	65 ± 7	64 ± 4	65 ± 6	60 ± 6	62 ± 7	
Ventricular threshold, V	0.55 ± 0.25	0.50 ± 0.29	0.75 ± 0.4	0.58 ± 0.27	0.60 ± 0.33	0.84 ± 0.58	0.74 ± 0.34	0.75 ± 0.43	1.4 ± 0.6**	
Ventricular lead impedance, Ohm	484 ± 65	367 ± 51*	295 ± 62**	430 ± 58	350 ± 48*	390 ± 21	504 ± 79	390 ± 14*	440 ± 36	
AV - delay, ms	AV-paced	168 ± 24	172 ± 28	208 ± 35	194 ± 36	200 ± 53	170 ± 45	232 ± 23	175 ± 27	220 ± 28
	AV-sensed	124 ± 25	130 ± 23	186 ± 60	130 ± 21	136 ± 27	154 ± 45	146 ± 31	155 ± 36	200 ± 48
Ventricular pacing, %	96.4 ± 11.6	97.8 ± 12.1	97.4 ± 4.8	94.5 ± 15.6	95.3 ± 15.8	93 ± 34	98.2 ± 10.9	99.3 ± 11.8	99 ± 11.3	
Atrial fibrillation/flutter time, %	3 ± 0.1	2 ± 0.2	2 ± 0.2	10 ± 4	11 ± 5	11 ± 6	31 ± 21	17 ± 13*	15 ± 8	

* $p < 0.05$ – significant differences of pacing parameters in different QRS complex classes after 6 month of permanent pacing vs. early postoperative period

** $p < 0.05$ – significant differences of pacing parameters in different QRS complex classes after one year vs 6 month follow-up

Basic pacing frequency, stimulated and detected AV-delay, as well as the percentage of ventricular pacing did not depend on QRS complex duration class and retain their values in all observation stages.

Ventricular pacing threshold were not

changed in the first 6 months in any of the QRS complex duration classes, but was increased at the annual observation stage in class 3 ($p < 0.05$).

Ventricular lead impedance in the first six months was decreased in all QRS complex

duration classes and then was stabilized at the annual observation stage in classes 2 and 3, meanwhile it was continued to decrease in class 1.

Atrial fibrillation/flutter time was initially higher in class 3 than classes 1 and 2. In six months observation stage this value has not changed in classes 1, 2 and was decreased in class 3 ($p < 0.05$), but did not reach the values of class 1 and 2. Atrial fibrillation/flutter time in annual observation stage was not changed within the classes against the six month period.

Absence of change of basic pacing rate, stimulated and detected AV-delay, as well as percentage of ventricular pacing at all observation stages does not depend on the QRS complex duration and indicates the reaching of the optimal values already in the early postoperative period.

Raising of ventricular threshold at the annual observation stage in patients of QRS complex duration class 3 might can be attributed to greater atherosclerosis frequency what was shown earlier (14 % in patient with QRS complex duration more than 120 ms vs. 3 % less than 120 ms) [1].

Levine P.A. et al. [2] associated pacing threshold raising at deferred observation stages with the formation of connective tissue scar at the electrode-myocardium region. Our study suggests that these changes are more prominent in patients of QRS duration complex class 3.

We could suspect that the reduction of ventricular pacing lead impedance is caused by so-called «maturation» of the electrode. Data on more pronounced decrease in the impedance in the shorter QRS complex are

consistent with Mitov V. et al [3].

Reducing of atrial fibrillation/flutter time in class 3 of QRS complex duration approach to that of patients of 1, 2 can be attributed to the optimization of medical management of patients with a permanent pacemaker [4, 5].

CONCLUSIONS

1. Basic pacing frequency and AV-delay, as well as the percentage of ventricular pacing is not related to QRS complex duration classes and do not change at observation stages of permanent pacing.

2. Ventricular pacing threshold, ventricular lead impedance and atrial fibrillation/flutter time in the annual observation stage defines the QRS complex duration class: ventricular pacing threshold in the first six months of observation was not changed in any of classes and was increased the annual stage in the class 3, ventricular lead impedance was decreased in the first six months in all classes, and it was stabilized in annual observation stage in class 2 and 3 and was continued to decline in class 1, atrial fibrillation/flutter time was initially higher in class 3, in six months stage was decreased without reaching, however, the values in class 1 and 2.

3. Ventricular pacing threshold, lead impedance and atrial fibrillation/flutter time can be used in the control of management patients with pacemakers

PROSPECTS FOR FUTURE STUDIES

It seems appropriate further investigation of possibility of management optimization taking into account QRS complex duration in patients with implanted pacemaker.

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Clinical case

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EFFECTIVENESS OF BIOFEEDBACK IN A CLOSED LOOP OF HEART RATE VARIABILITY PARAMETERS AND PACED BREATHING IN PATIENTS WITH ARTERIAL HYPERTENSION IN REAL CLINICAL PRACTICE

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On example of clinical analysis of two comparable in all parameters patients with arterial hypertension application of biofeedback (BFB) in the closed loop of heart rate variability (HRV) and paced breathing was evaluated. Both patients received standard medical therapy according to the guidelines of the Association of Cardiologists of Ukraine, in patient 1 additionally was conducted 10 sessions of BFB in investigated loop. Effectiveness of the proposed method was evaluated by comparing the values of systolic, diastolic, pulse blood pressure (SBP, DBP and PD, respectively) and integral indicator of regulatory systems' state - BQI index within 10 days from starting treatment. Supplement of standard pharmacotherapy by biofeedback sessions in closed loop of HRV and paced breathing is significantly better than isolated drug treatment in the control of SBP, DBP and PD due to optimization of regulatory systems' state. Obtained data allow to recommend this technique in clinical practice.

KEY WORDS: arterial hypertension, biofeedback, heart rate variability, paced breathing

ЕФЕКТИВНІСТЬ БІОЛОГІЧНОГО ЗВОРОТНОГО ЗВ'ЯЗКУ В КОНТУРІ ПАРАМЕТРІВ ВАРІАБЕЛЬНОСТІ СЕРЦЕВОГО РИТМУ І МЕТРОНОМІЗОВАНОГО ДИХАННЯ У ПАЦІЄНТІВ З АРТЕРІАЛЬНОЮ ГІПЕРТЕНЗІЄЮ В РЕАЛЬНІЙ КЛІНІЧНІЙ ПРАКТИЦІ

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На прикладі клінічного розбору двох, порівнянних за всіма параметрами, пацієнтів з артеріальною гіпертензією оцінено використання біологічного зворотного зв'язку (БОС) в контурі варіабельності серцевого ритму (ВСР) та метрономізованого дихання в реальній клінічній практиці. Обидва пацієнти отримували стандартну медикаментозну терапію відповідно до рекомендацій Асоціації кардіологів України, пацієнту 1 додатково проведено 10 сеансів БОС в досліджуваному контурі. Ефективність запропонованої методики оцінювалася на підставі порівняння значень систолічного, діастолічного, пульсового артеріального тиску (САТ, ДАТ і ПД, відповідно) і інтегрального індикатора стану регуляторних систем - індексу BQI протягом 10 днів від початку лікування. Доповнення стандартної фармакотерапії сеансами БОС в замкнутому контурі ВСР і метрономізованого дихання значно перевищує по ефективності ізольоване медикаментозне лікування в контролі САТ, ДАТ і ПД за рахунок оптимізації стану системи регуляції. Отримані дані дозволяють рекомендувати методику в клінічну практику.

КЛЮЧОВІ СЛОВА: артеріальна гіпертензія, біологічний зворотний зв'язок, варіабельність серцевого ритму, метрономізоване дихання

ЭФФЕКТИВНОСТЬ БИОЛОГИЧЕСКОЙ ОБРАТНОЙ СВЯЗИ В КОНТУРЕ ПАРАМЕТРОВ ВАРИАБЕЛЬНОСТИ СЕРДЕЧНОГО РИТМА И МЕТРОНОМИЗИРОВАННОГО ДЫХАНИЯ У ПАЦИЕНТОВ С АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ В РЕАЛЬНОЙ КЛИНИЧЕСКОЙ ПРАКТИКЕ

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На примере клинического разбора двух, сопоставимых по всем параметрам, пациентов с артериальной гипертензией оценено использование биологической обратной связи (БОС) в контуре variability сердечного ритма (ВСР) и метрономизированного дыхания в реальной клинической практике. Оба пациента получали стандартную медикаментозную терапию согласно рекомендациям Ассоциации кардиологов Украины, пациенту 1 дополнительно проведено 10 сеансов БОС в изучаемом контуре. Эффективность предложенной методики оценивалась на основании сравнения значений систолического, диастолического, пульсового артериального давления (САД, ДАД и ПД, соответственно) и интегрального индикатора состояния регуляторных систем – индекса BQI в течение 10 дней от начала лечения. Дополнение стандартной фармакотерапии сеансами БОС в замкнутом контуре ВСР и метрономизированного дыхания значительно превосходит по эффективности изолированное медикаментозное лечение в контроле САД, ДАД и ПД за счет оптимизации состояния системы регуляции. Полученные данные позволяют рекомендовать методику в клиническую практику.

КЛЮЧЕВЫЕ СЛОВА: артериальная гипертензия, биологическая обратная связь, variability сердечного ритма, метрономизированное дыхание

INTRODUCTION

Arterial hypertension (AH) is a serious, debilitating disease, which is not only medical but also social and economic problem worldwide: about 45 % of adults aged from 25 years old have high blood pressure, 74.3 % are aware about the disease, just 43 % are treated, efficacy of the treatment is only 13 % [1]. Key point of this disease is an imbalance of regulatory systems in the body with predominance of the sympathetic nervous system branch [2]. Low efficiency of pharmacotherapy boosted searching for non-drug methods [3]. Promising tool of adjunctive therapy in patients with AH can be biofeedback (BFB) in the closed loop of paced breathing under the control of heart rate variability (HRV) parameters [4]. In these comparable cases we want to show you effectiveness of this method in real clinical practice.

OBJECTIVE

Purpose of the research is to study the effectiveness of biofeedback in a closed loop of heart rate variability and paced breathing in two comparable in all parameters patients with arterial hypertension in real clinical practice.

MATERIALS AND METHODS

Patient 1

Male, 64 y/o, retired, lives in the city, admitted to the hospital in November 2014.

Complaints on admittance: periodical increase of BP up to 150/95 mm Hg, usually in the morning, followed by headache in occipital area and/or dizziness.

Anamnesis morbi: Arterial hypertension since 2000 with maximum BP 155/95 mm Hg. Usual BP 120-130/70-80 mm Hg. Multiple

hospitalizations and treatment in outpatient clinic. Previous hospitalization in November 2013, after discharge ignored prescribed treatment. Current hospitalization due to complaints described above.

Anamnesis vitae: Appendectomy in young age. Tuberculosis, diabetes mellitus, STD, viral hepatitis, rheumatism, psychiatric diseases in the anamnesis denies. No pernicious habits. No alcohol abuse. Heredity is uncomplicated. No allergic reactions in the past.

Status presence objectivus: Patient's overall condition is satisfactory, consciousness is clear, position is active. Ectomorph body type. Growth 175 cm, weight 68 kg, waist 90 cm, BMI 22,0 kg/m². Skin and visible mucous are pale-pink, clear. Peripheral lymph nodes are not enlarged. Thyroid gland can't be palpated. Skeletal-muscular system without features. Respiratory system: clear lung sound during percussion, vesicular breathing during auscultation without additional sounds. Cardiovascular system: heart rate is rhythmic, tones are muffled, accent of the S2 on aorta. HR = pulse = 65 bpm. BP 150/95 mm Hg. Abdomen is normal in size, soft and painless during palpation. Liver under the edge of ribs arch, painless. No peripheral edema.

Patient 2

Male, 60 y/o, retired, lives in the city, admitted to the hospital in October 2014.

Complaints on admittance: episodic increase of BP up to 150/90 mm Hg, usually in the morning, which followed by headache in frontal and temporal areas.

Anamnesis morbi: Arterial hypertension since 1995 with maximum BP 155/95 mm Hg. Usual BP 120/70 mm Hg. Multiple hospitalizations and treatment in outpatient

clinic. Previous hospitalization in January 2014, after discharge regularly took indapamide 2,5 mg in the morning. Current hospitalization due to same complaints.

Anamnesis vitae: Right wrist joint fracture in 1983. Tuberculosis, diabetes mellitus, STD, viral hepatitis, rheumatism, psychiatric diseases in the anamnesis denies. No pernicious habits. No alcohol abuse. Heredity is uncomplicated. No allergic reactions in the past.

Status presence objectivus: Patient's overall condition is satisfactory, consciousness is clear, position is active. Ectomorphic body type. Growth 170 cm, weight 60 kg, waist 84 cm, BMI 21,0 kg/m². Skin and visible mucous are pale-pink, clear. Peripheral lymph nodes are not enlarged. Thyroid gland can't be palpated. Skeletal-muscular system without features. Respiratory system: clear lung sound during percussion, vesicular breathing during auscultation without additional sounds. Cardiovascular system: heart rate is rhythmic, tones are muffled, accent of the S2 on aorta. HR = pulse = 68 bpm. BP 150/90 mm Hg. Abdomen is normal in size, soft and painless during palpation. Liver under the edge of ribs arch, painless. No peripheral edema.

INVESTIGATION PLAN IN THE HOSPITAL

- Clinic blood count
- Urinalysis
- Biochemical blood test (bilirubin, ALT, AST, glucose, creatinine, Na, K)
- Lipid profile
- Chest x-ray
- ECG
- Heart ultrasound with Doppler
- Kidneys ultrasound with Doppler
- Ophthalmologist consultation

INVESTIGATION RESULTS

Clinic blood count: indexes are in normal range in both patients.

Urinalysis: indexes are in normal range in both patients.

Biochemical blood test: indexes are in normal range in both patients.

Lipid profile: indexes are in normal range in both patients.

Chest x-ray: normal in both patients.

ECG: patient 1: sinus rhythm, regular, HR 61 bpm, hypertrophy of myocardium of left ventricle by wave's ratio criterion; patient 2: sinus rhythm, regular, HR 64 bpm,

hypertrophy of myocardium of left ventricle by wave's ratio criterion.

Heart ultrasound with Doppler: patient 1: hypertrophy of myocardium of left ventricle (LV posterior wall thickness: 12 mm, interventricular septum: 11,8 mm), systolic function is preserved (EF = 61 %); patient 2: hypertrophy of myocardium of left ventricle (LV posterior wall thickness: 12,3 mm, interventricular septum: 12,0 mm), systolic function is preserved (EF = 64 %).

Kidneys ultrasound with Doppler: patient 1: incomplete doubling of left kidney, micro urolithiasis; patient 2: microurolithiasis.

Ophthalmologist consultation: patient 1: angiopathy of retinal vessels of both eyes; patient 2: Angiopathy of retinal vessels of both eyes.

CLINICAL DIAGNOSIS

Patient 1: Arterial hypertension II stage 1 degree, HF 0 stage, moderate additional risk.

Patient 2: Arterial hypertension II stage 1 degree, HF 0 stage, moderate additional risk.

TREATMENT

Lifestyle modification: control of body weight, diet, regular exercises.

Drugs therapy: perindopril 5 mg 1 time per day in the evening, aspirin-cardio 100 mg in the evening.

Non-drug therapy: patient 1 – 10 biofeedback sessions in the loop of paced breathing under the control of heart rate variability parameters; patient 2 – 10 pseudosessions without inclusion of feedback under the control of heart rate variability parameters.

Biofeedback sessions were performed on a computer diagnostic complex «CardioLab2009» («XAI-Medica») with additional custom module «Biofeedback», including software related audible and visual breathing metronome and dynamic algorithm for determining the current value of HRV indices, changed under paced breathing influence.

HRV parameters were estimated in slide buffer for 1 minute through dynamic spectral decomposition by fast Fourier transform of R-R intervals sequence of lead I ECG records with 1000 Hz digitization frequency. All calculations were conducted in real-time during 7-minute biofeedback session. Power of low (V, up to 0,05 Hz), medium (L, 0,05-0,15 Hz) and high

(H, 0,15-0,40 Hz) HRV parameters were estimated, then they were transformed into two-dimensional coordinate space with L/H and V/(L+H) axes, which correspond to power of sympathovagal and neurohumoral balances of regulation [5].

During biofeedback session, initialization of adaptation algorithm of biofeedback module was conducted in first 2 minutes, when patient breathe in his normal rhythm. After that for each following minute exact frequency of paced breathing was set through frequency rearrangement of aural-visual breathing metronome. Adaptation algorithm consists in automatic seeking of such frequency, when current L/H and V/(L+H) values are maximally approximate to optimum zone [6].

Efficacy of biofeedback was evaluated by comparing the values of systolic, diastolic and pulse blood pressure (SBP, DBP and PP, respectively); BQI integral index – parameter

that reflects all qualitative changes of biofeedback process: optimality (O, estimation of farness of regulatory systems from optimal state during whole period of session), sensitivity (S, estimation of receptivity of regulatory systems to paced breathing), effectiveness (E, estimation of approaching range of HRV parameters to optimal physiological state during execution of optimal bioreverse control algorithm) [7].

Statistical analysis of the results for each subject was carried out using Microsoft Excel computer software.

RESULTS AND DISCUSSION

Dynamic of SBP, DBP, and PP in both patients on background of the treatment presents in fig.1. During the same treatment in both patients systemic biofeedback implementation contributed to lower values aforementioned indices.

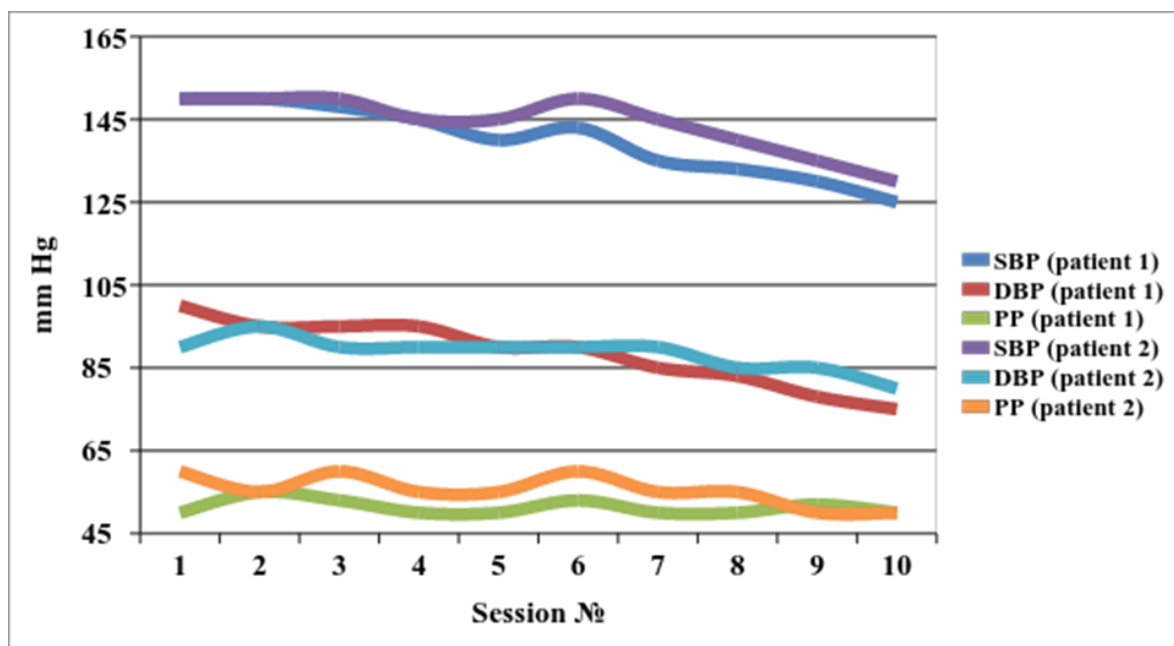


Fig.1. SBP, DBP, and PP dynamic in both patients during the treatment

BQI index dynamic in both patients during 10 sessions presents in fig.2. Systematic biofeedback sessions in patient 1 contributed natural approximation of regulation to the

optimal level, whereas in patient 2 it index fluctuated within suboptimal level without reaching the target level.

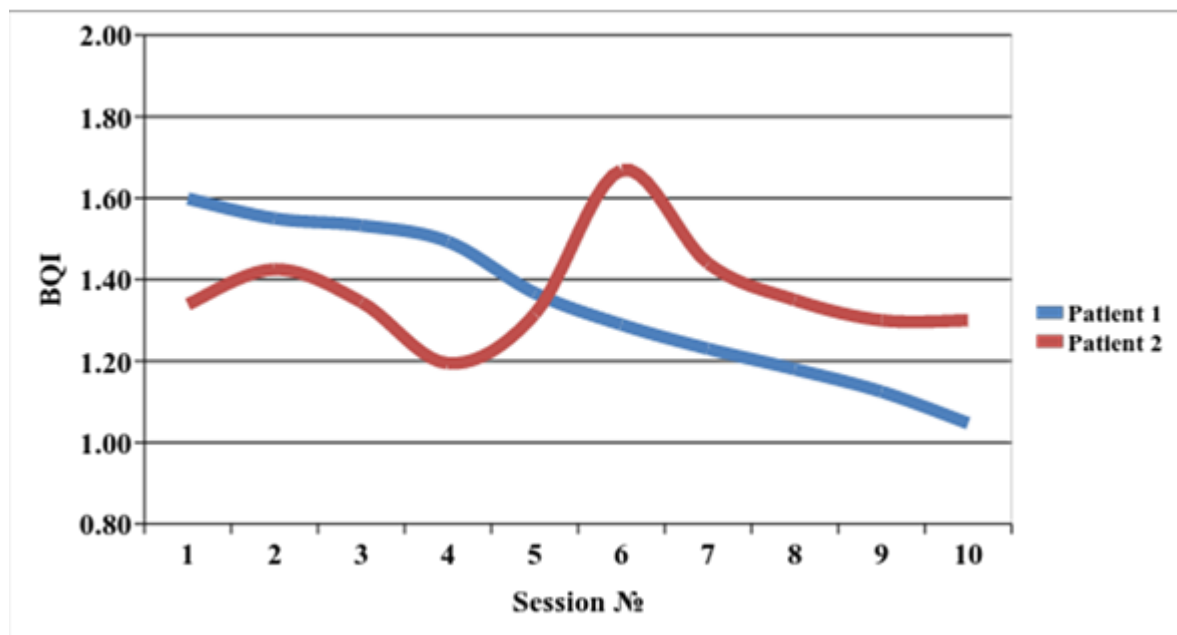


Fig.2. BQI index dynamic in both patients during 10 days of treatment

Arterial hypertension is the most common chronic disease among adults [1]. Pharmacotherapy still does not allow to reach optimum level of blood pressure in some patients that stimulated the development of non-drug methods of treating [3].

Biofeedback with a contour of HRV and paced breathing is one of the promising methods for increase of blood pressure controllability [4]. Supplement of standard pharmacotherapy by biofeedback sessions in closed loop of HRV and paced breathing is significantly better than isolated drug treatment in the control of SBP, DBP and PD due to optimization of regulatory systems' state. The effectiveness of biofeedback in a closed loop of heart rate variability and paced breathing allows us to recommend it as a component of complex therapy for patients with arterial hypertension.

CONCLUSIONS

1. Biofeedback in a closed loop of heart rate variability and paced breathing allow to optimize the regulatory systems condition of the body in patients with arterial hypertension.
2. Combination of biofeedback sessions and drug treatment is significantly superior in effectiveness of the isolated pharmacological therapy.
3. The effectiveness of biofeedback in a closed loop of heart rate variability and paced breathing allows us to recommend it as a component of complex therapy for patients with arterial hypertension.

PROSPECTS FOR FUTURE STUDIES

It is interesting to evaluate the effectiveness of biofeedback sessions in the investigated loop in patients with arterial hypertension depending from the stage and degree of the disease.

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POLYCYTHEMIA VERA AN EXAMPLE OF A CLINICAL CASE

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The article concerns a clinical case management of patients with polycythemia vera. The data are given from the laboratory and instrumental diagnostic methods, clinical diagnosis, selection of the optimized treatment and modification of the habit of life.

KEY WORDS: polycythemia vera, secondary arterial

ІСТИННА ПОЛІЦИТЕМІЯ НА ПРИКЛАДІ КЛІНІЧНОГО ВИПАДКУ

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Розглянуто клінічний випадок ведення пацієнта з істинною поліцитемією. Наведені дані лабораторних та інструментальних методів дослідження, описана діагностика, постановка клінічного діагнозу, вибір оптимальної тактики лікування та модифікація способу життя.

КЛЮЧОВІ СЛОВА: істинна поліцитемія, вторинна артеріальна гіпертензія

ИСТИННАЯ ПОЛИЦИТЕМИЯ НА ПРИМЕРЕ КЛИНИЧЕСКОГО СЛУЧАЯ

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Рассмотрен клинический случай ведения пациента с истинной полицитемией. Приведены данные лабораторных и инструментальных методов исследования, описана диагностика, постановка клинического диагноза, выбор оптимальной тактики лечения и модификация образа жизни.

КЛЮЧЕВЫЕ СЛОВА: истинная полицитемия, вторичная артериальная гипертензия

INTRODUCTION

Polycythemia vera or erythremia, Vaquez disease – is a chronic neoplastic myeloproliferative disorder with bone marrow involvement on the cell level, precursor of myelopoiesis, characterized by the unbounded proliferation of all three hematopoietic lineages, which predominantly are erythroid and megakaryocytic, granulocytic in a smaller extent [1, 2].

The disease is quite rare: 0,5-1,7 cases per 100,000 in full set population [3].

The main difficulty and danger pose that the disease is most commonly developed over the years (an average of 15 –20years) with a gradual increase of symptoms, that all this time has not been specific to such a disease. This

leads to the late diagnosis and treatment, which results in the reduced quality of life of the patient. That poses a danger of the sequel occurrence, such as: myocardial infarction, the stroke, the syndrome of the disseminated intravascular coagulation and others [1-3].

Thus, such factors necessitate early detection of polycythemia vera cases and their forehanded treatment. This article focuses on one of such cases.

CLINICAL CASE

The patient I., a man born in 1983, was admitted to the CCH UZ cardiology department in October, 2013 with complaints about general weakness, periodic headache of pressing nature, often perceiving in the temporal regions and accompanied by noise in

the ears; dizziness accompanied by the increased blood pressure; pains in chest of compressive, heating character without irradiation and dependence on any physical activity, compensated spontaneously after 5-10 minutes of its occurrence.

HISTORY OF DISEASE

Such complaints for the first time occurred in the spring of 2013. In October 2013 at a time when emerged intense headache, it had been registered the increasing numbers of the blood pressure to 180/110 mm Hg, that was the reason why he had been hospitalized in one of the city hospitals. Received therapy: magnesia, Dibazolom tablets without any positive effect. By agreement, the patient was transferred to Ukrainian railway central clinical hospital (CCH UZ) cardiology department for further examination and treatment. Additionally cases of nosebleeds on a background of normal blood pressure were diagnosed.

ANAMNESIS VITAE

Leads a healthy lifestyle, patient does not smoke or drink, getting enough nutrition, has good living conditions. Grew and developed according to the sex and age. There are no injuries and surgical operations occurred in the past. In the childhood suffered the chickenpox. Hereditary and allergic anamneses are not burdened. Viral hepatitis, tuberculosis, venereal diseases, diabetes mellitus, HIV are absent.

PHYSICAL EXAMINATION

General condition is satisfactory, conscience is clear, position is active. The body type is normosthenic. Skin is clean, normal colored, without any scars, traces of scratching and venous lakes, moderate hyperemia of the cheeks is observed, visible mucous membranes of pale pink color, derivatives of the skin are without any visible changes. There is no edema. Subcutaneous fat tissue is developed satisfactorily, uniformly, respectively to the sex and age. Peripheral lymph nodes are not enlarged, with normal consistency. Thyroid gland isthmus is palpable. Musculoskeletal system is without any singularities. Auscultation over the lungs is clear, vesicular breathing. The heart rhythmical sounds are clear, heart rate - 67 beats/min, blood pressure - 150 /90 mm Hg. Abdomen is normally sized, soft and painless. Liver and

spleen remain impalpable. Tapping symptom is negative on both sides.

REFERRAL DIAGNOSIS

Somatoform autonomic dysfunction

RESULTS OF LABORATORY AND INSTRUMENTAL DIAGNOSIS

All the represented testing was conducted on the basis of CCH UZ in October, 2013.

Complete blood count: polychromemia 179 g/L, erythremia $5.67 \times 10^{12}/L$, increased hematocrit 51.1, other indices are within normal limits.

Biochemical analysis of blood: imperceptible hypercholesterolemia 5.62 mmol/L, other indices within normal limits.

Electrocardiography (ECG) showed regular sinus rhythm, heart rate (HR) 73 beats per minute, axis deviation to the left.

Veloergometry: the total amount of work done 5508 kgf (54.02 kJ), the power load maximum proposed 150 V, complaints during the test of general fatigue, the reason for stopping is the achievement of submaximal heart rate, during the trial and recovery period the ECG did not show any coronary insufficiency. The test is negative.

Holter ECG and blood pressure monitoring: monitoring showed regular sinus rhythm with average HR 73 beats per minute, paroxysmal arrhythmias and any ischemic changes are not diagnosed. During the day and the night indices of systolic blood pressure and diastolic blood pressure are typical for normotension. Average BP is 108/64 mmHg.

Echocardiography: abnormal chord were diagnosed in the left ventricular, myocardial hypertrophy of the left ventricular, no akinesia zones have been identified, the indicators of myocardial contractility of the left ventricle are saved.

Ultrasound of the kidneys, adrenal glands and bladder: increased blood flow velocity in distal thirds of the renal arteries.

Check ultrasound of the renal arteries showed no clear data of the significant dopplerographic hemodynamic narrowing of the renal arteries on both sides.

Ultrasound of the thyroid gland: increased echogenicity, diffuse changes in the thyroid gland.

Ultrasonography of the abdomen: diagnosed liver and pancreas diffuse changes.

Consultation of neurologist: Dysfunction of autonomic nervous system.

Has been carried the brain magnetic resonance imaging (MRI): MRI of the brain did not diagnose any organic pathology.

RECOMMENDATIONS FOR FURTHER EXAMINATION

Complete blood count with the diagnosis of serum erythropoietin (in favor of polycythemia vera there would be indicated the plethora on the background of normal or even low concentration of serum erythropoietin).

Determination of blood oxygen saturation for diagnosing with secondary erythrocytosis (in favor of polycythemia vera there would be indicated normal blood oxygen saturation - more than 92 %).

Determining whether a mutation V617F persists in the gene JAK2, which is etiological factor of polycythemia vera. Consultation with the hematologist to clarify the diagnosis [4].

Lipidogram.

Thyroid panel determination of TSH, T3, T4 [5, 6].

BASIC CLINICAL SYNDROMES

- Pletorhycal: erythrocythaemia, arterial hypertension, headaches.
- Hyper blood viscosity with the microcirculation disorders: anginal aches and headaches.

CLINICAL DIAGNOSIS

First stage of polycythemia vera: of a few symptoms up to 5 years [2, 3].

Secondary arterial hypertension, II stage - with the presence of objective evidence of target organ damage without symptoms on their part or dysfunction - left ventricular hypertrophy, moderate 3 degree hypertension with systolic figures of blood pressure between 160 and 179 mm Hg, heart failure is absent [7].

CASE MANAGEMENT

At one of the hospital's department, before the establishing diagnosis, the patient has been treated as follows:

1. Noliprel (perindopril arginine + indapamide) tab. 1. morning 5/1.25mg.
2. Pentilin (pentoxifylline) 5.0 ml / in cap.
3. Eufillin 5.0 ml of 2 % + 50 % Analginum 2.0 ml / cap.
4. Noobut (Phenibutum) 250mg, 1 tab. 2 times a day.

5. Lysine aescinat 0.1 % 5.0 ml / intven. drip.

6. Relaxil (hydroalcoholic extract of dry valerian 0.8 % + dry mint peppermint + Melissa extract dry) 1 capsule (0.125 / 0.025 / 0.025) 2 t / d.

7. Psychotherapy.

8. Therapeutic exercise.

9. Physiotherapy.

RECOMMENDATIONS FOR TREATMENT AFTER DIAGNOSIS

1. Bloodletting (phlebotomy): effusion of 200-300 ml, every day or every second day to achieve the target hematocrit level - 0.42-0.45.

2. At run time of phlebotomy - taking aspirin (100 mg / day).

3. Angiotensin converting enzyme inhibitor (perindopril) 2 mg/day under the control of blood pressure (at home), after 2 weeks-checking visit to correct the dose.

Due to a significance of combination of various risk factors on the development of disease, a term risk factors has been accepted for general use instead of a singular risk factor term. To evaluate the effect of risk factors on the prognosis, the course, and the outcomes of the disease, it is important to introduce a global index as an integral measure [8].

RECOMMENDATIONS FOR LIFESTYLE MODIFICATION

Bring in the diet following principles of sensible nutrition:

1. Reduce intake of fats by one-third, mainly due to saturated ones.
2. Increase mono- and polyunsaturated fatty acids in nutrition.
3. Increase consumption of fruits and vegetables, rich in potassium and magnesium.
4. Limit the usage of salt.

Aerobic exercise of moderate intensity: jogging, swimming, cross-country skiing, biking.

PROGNOSIS

Polycythemia vera is a chronic disease, hence the prognosis relatively recovery is poor. But considering the detection of the disease at early stages, as well as previously initiated treatment, the prognosis for the patient's life is favorable. It should be mentioned that without any treatment mortality within 18 months after the diagnosis of the disease is about 50 %. With adequate and timely therapy the median

survival exceeds 10 years, the patients of young and middle-age – several decades.

The most common cause of death is thrombosis, the second by importance - complication of myeloid metaplasia with the transition of the disease in leukemia, therefore the further case of the patient is to be directed

concerning these two aspects. For the first it is disaggregated control therapy of thrombosis and it's further consequences. For the second case, unfortunately, at this stage there is taken no precaution, though timely started treatment will provide a benign clinical course of the disease [1-4].

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TREATMENT OF ARTERIAL HYPERTENSION AND QTc INTERVAL DURATION THROUGH CLINICAL PRACTICE

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This clinical case presents the treatment of arterial hypertension (AH) with improvement levels of daily average blood pressure (BP) in comparison with the initial level at the background of increasing the proportion of elongated corrected interval QTc and a violation of the average daily profile. The patient K. receiving ramipril in the morning 5 mg and 10 mg evening after 3 months during the control of daily monitoring of BP and ECG there is a decrease of average daily SBP and DBP daily average. Normalization of the average daily profile of DBP from «excessive degree of nocturnal BP reduction «in the» normal degree of nocturnal BP reduction». At the same time, however, there is an increase in the number of episodes of lengthening the interval corrected QTc and increase the proportion of elongated corrected interval QTc as well as the conversion of the average daily profile SBP «excessive degree of nocturnal BP reduction» in the «insufficient degree of nocturnal BP reduction», which increases the risk of acute cardiovascular events and requires further adjustment of therapy. This case demonstrates the individual patient's response to antihypertensive therapy in view of increased psycho-emotional stress associated with the specifics of her work.

KEY WORDS: arterial hypertension, ambulatory blood pressure monitoring, ECG monitoring, the insufficient degree of night BP decrease, excessive degree of nocturnal BP reduction, normal degree of nocturnal BP reduction

ТЕРАПІЯ АРТЕРІАЛЬНОЇ ГІПЕРТЕНЗІЇ І ТРИВАЛІСТЬ ІНТЕРВАЛУ QTc ЧЕРЕЗ КЛІНІЧНУ ПРАКТИКУ

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Описано клінічний випадок терапії гіпертонічної хвороби з поліпшенням середньодобових цифр АТ порівняно з початковим рівнем на тлі підвищення питомої ваги подовженого коригованого інтервалу QTc і порушенням середньодобового профілю. У пацієнтки К. на фоні прийому раміприлу 10 мг вранці і 5 мг ввечері через 3 місяці при проведенні контрольного добового моніторингу АТ та ЕКГ відзначається зниження середньодобового САТ і середньодобового ДАТ. Нормалізація середньодобового профілю ДАТ з «надмірного нічного зниження АТ» до «нормального ступеню нічного зниження АТ». При цьому, проте, відзначається збільшення числа епізодів подовження коригованого інтервалу QTc і підвищення питомої ваги подовженого коригованого інтервалу QTc, а також конвертація середньодобового профілю САТ з «надмірного нічного зниження АТ» до «недостатнього ступеню нічного зниження АТ», що збільшує ризик гострих серцево-судинних подій і вимагає подальшої корекції терапії. Даний клінічний випадок демонструє індивідуальну відповідь пацієнтки на гіпотензивну терапію з урахуванням підвищеного психоемоційного навантаження, що пов'язано зі специфікою її роботи.

КЛЮЧОВІ СЛОВА: гіпертонічна хвороба, добове моніторування артеріального тиску, добове моніторування ЕКГ, недостатня ступінь нічного зниження АТ, надлишкова ступінь нічного зниження АТ, нормальна ступінь нічного зниження АТ

ТЕРАПІЯ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ И ПРОДОЛЖИТЕЛЬНОСТЬ ИНТЕРВАЛА QTc ЧЕРЕЗ КЛИНИЧЕСКУЮ ПРАКТИКУ

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Описан клинический случай терапии гипертонической болезни с улучшением среднесуточных цифр АД по сравнению с исходным уровнем на фоне повышения удельного веса удлиненного

корректированного интервала QTc и нарушения среднесуточного профиля. У пациентки К. на фоне приема рамиприла 10 мг утром и 5 мг вечером через 3 месяца при проведении контрольного суточного мониторирования АД и ЭКГ отмечается снижение среднесуточного САД и среднесуточного ДАД. Нормализация среднесуточного профиля ДАД с «чрезмерного ночного снижения АД» до «нормальной степени ночного снижения АД». При этом, однако, отмечается увеличение числа эпизодов удлинения корректированного интервала QTc и повышение удельного веса удлиненного корректированного интервала QTc, а также конвертация среднесуточного профиля САД с «чрезмерного ночного снижения АД» до «недостаточной степени ночного снижения АД», что увеличивает риск острых сердечно-сосудистых событий и требует дальнейшей коррекции терапии. Данный клинический случай демонстрирует индивидуальный ответ пациентки на гипотензивную терапию с учетом повышенной психоэмоциональной нагрузки, что связано со спецификой ее работы.

КЛЮЧЕВЫЕ СЛОВА: гипертоническая болезнь, суточное мониторирование артериального давления, суточное мониторирование ЭКГ, недостаточная степень ночного снижения АД, избыточная степень ночного снижения АД

INTRODUCTION

The duration of the QTc interval is not just electrophysiological phenomenon, but the most important parameter characterizing the electric systole of the heart [1]. Its shortening and lengthening reflect gross violations of the heart, which are associated with the risk of severe clinical syndromes including sudden cardiac death. Its reaction to the drug candidate determines be it so or not.

Clinical practice has deal with real patients, each of which can respond and responds to the already approved and included in the standard of care drugs, and these reactions may differ materially from those anticipated according to instructions attached to it.

That this is so, and that in clinical practice, the physician is obliged to rely not on the instructions but on patient's response to drug was demonstrated by our clinical case.

CLINICAL CASE

Patient K., 50 years old, lives in Kharkiv, works as supervisor in extracurricular institutions for over 15 years.

Complaints during the initial examination: recurrent headaches with pressing nature often in the occipital region against the backdrop of increasing blood pressure to 160/90 mmHg, associated with emotional stress or weather condition.

Constant tinnitus, which get worse in the middle of the day. Periodical pressing pain in the heart after emotional stress without irradiation, accompanied by numbness of the left hand fingers. All symptoms are relieved by exercise (walking). Drug therapy is not accepted.

Periodical strong compressive pain in the middle and lower third of the sternum, burning sensation associated with psycho-emotional stress and without connection with food intake.

Periodical hunger pains. Bitterness in the morning, heaviness in the right upper quadrant.

History of the disease: first time high blood pressure (BP) was mentioned in 1995 during second pregnancy. For 16 years BP control was absent. In 2011 was fixed high blood pressure after a strong stress. Maximum level was 180/110 mmHg. Treatment in day hospital: ramipril 5 mg, bisoprolol 2,5 mg, polokard 75 mg, mildronate 5,0 ml.

Until July 2014 she was not treated. Sometimes she registered increasing of blood pressure to 160/100 mmHg. Periodically taking ramipril 5mg in the morning.

Life history: born in a large city, second child in the family. Sexual development is according to her age. Start working in 17 years old. Working and living conditions are satisfactory. The nature of the work is associated with increasing of emotional load. Lifestyle is satisfactory. Married. Has 2 children.

Postponed diseases: chickenpox, measles, mumps, cold, tonsillitis, acute bronchitis, pneumonia, primary varicose expansion of right saphenous vein, chronic cholecystitis, cholelithiasis, esophagitis.

Injuries are denied. In 1996 was removed uterus with appendages due to bleeding during second delivery.

Tuberculosis, viral hepatitis, sexually transmitted diseases are denied.

Family history of diabetes mellitus, cancer, mental illness, tuberculosis is not burdened.

Mother in 19 years old was operated because of thyroid goiter, she has AH for 20 years. Her mother, grandmother and aunt on the maternal line suffered from acute ischemic stroke. Mother suffered from malaria in childhood.

Her father had chronic gastritis with low acidity. In 65 years old 2/3 of the stomach was removed due to polyps. More than 50 years he smoked about 2 packs of cigarettes a day, drank alcohol. Blood pressure was low.

Allergic anamnesis is not burdened.

She does not have bad habits.

Objective examination: general condition was relatively satisfactory. Skin and visible mucous membranes was clean, normal in color. Peripheral lymph nodes were not enlarged. Weight gain: weight - 95 kg, height - 164 cm, BMI - 35.3, waist - 103cm.

Heart sounds were muffled, rhythmic, accent of 2 tone on the aorta, heart rate - 86 beats/min, BP - 150/100 mmHg. In the lungs was vesicular breathing. Tongue was clean, damp. Abdomen was soft on palpation, painless, increased in size due to the subcutaneous fat. There was moderate pain in the thoracic region of the spine during palpation.

Symptom effleurage on the lumbar region was negative on both sides. Physiological functions were normal. Peripheral edema did not present.

CVD risk factors: overweight, family history of cardiovascular disease in mother.

SPECIAL INVESTIGATIONS

Complete blood count (24/10/2014): all figures were in normal range.

Urinalysis (10/24/2014): all figures were in normal range.

Biochemical analysis indicators (09.07.2014) were in normal range, except blood sugar - 5.69 mmol/L (normal 3.33 - 5.55 mmol/L).

Glycosylated Hb (24.10.2014g.) was 6.4 mkmol fructose/g Hb (normal rate 3.5 - 7.0 mkmol fructose/g Hb).

Glucose tolerance test (20.03.2015g.): glycaemia on empty stomach - 6.16 mmol/L (venous blood); 2 hours after glucose load - 7.47 mmol/l.

In lipid profile (10/24/2014) was noted increasing level of total cholesterol, low density lipoprotein (LDL), atherogenic factor, and decreasing of high-density lipoprotein

(HDL). The results are summarized in table 3. The risk of fatal cardiovascular event according to SCORE scale is 1 %.

Ultrasound of the heart (08/10/2014): left ventricular hypertrophy (LVMH), additional chord in the apical segment of the left ventricle, ejection fraction (LVEF) - 57 % (normal rate 55 - 80 %).

Ultrasound of abdomen and kidneys (11/06/2013): cholelithiasis (calculus to 5 mm in diameter), uric acid diathesis.

Fibrogastroscopy (11/06/2014): catarrhal gastritis, surface duodenopathies.

ECG (02/10/2014): sinus rhythm, right, heart rate - 76 beats/min, electrical axis of heart was horizontal, moderate signs of left ventricular hypertrophy were present. The length of the waves on ECG were P - 114 ms, PQ - 146 ms, QRS - 84 ms, QT - 392 ms, QT corrected (QTc) - 442 ms.

On the basis of home blood pressure monitoring for 3 weeks (from 10.10.2015 to 03.11.2015) the average figures of BP in the morning were from 140/100 mm Hg up to 160/110 mm Hg, on the evening - from 130/90 mm Hg up to 150/110 mm Hg. Taking into account these home monitoring for patient was assigned ramipril 5 mg in the morning and 5 mg in the evening.

Daily monitoring of ECG and blood pressure (05/11/2014) [2-4].

During the daily monitoring, average figure of BP was 144/85 mm Hg and heart rate - 81 beats/min. Elevated systolic blood pressure (SBP), more than 135 mmHg in the daytime and 120 mmHg at night was during 68 % of the daily monitoring time, including 80 % in the daytime and 27 % at night. Normal SBP was in 31 % of the daily monitoring, 20 % in the daytime and 67 % at night. Elevated diastolic blood pressure (DBP), more than 85 mmHg in the daytime and 70 mmHg at night was recorded over 60 % of daily monitoring time, including 68 % in the daytime and 33 % at night. Normal DBP was in 40 % of the daily monitoring time, including 32 % in the daytime, 67 % at night. Reduction degree of blood pressure at night above normal, SBP - 23,1 % - «overdipper» [5], DBP - 23.8 % (normal 10-20 %) in background of using ramipril 5 mg in the morning and 5 mg in the evening. Results of ABPM presented in table 1, 2.

During ECG monitoring average heart rate was 76 beats/min (day - 84 beats/min, night -

65 beats/min). It has been recorded 156 episodes of sinus tachycardia, total duration - 3 hour 6 min (153 in daytime and 3 at night) with average heart rate in an episode of 97 beats/min and maximum heart rate to 139 beats/min during daytime hours (14:25:55) at the end of the meal. Minimum heart rate was 51 beats/min in the early morning hours (6:35:55). Most episodes of tachycardia were an adequate response to emotional and physical stress and were registered in the period of wakefulness. Circadian index was in the normal range - 1,30. During the period of observation in sinus rhythm was registered single ventricular extrasystoles, total number - 17 and single supraventricular arrhythmias, total number - 13. Episodes of ST-segment depression with total duration of 21 minutes were registered. During the day (14:28:45), at the end of the meal, on the background of an episode of tachycardia (heart rate - 118 beats/min) an episode of ST segment depression (-147mkV) during 12 min 30 sec was registered. It was recorded 26 episodes of lengthening corrected QTc interval, which occupying 32 % of the registration period time. The average length of corrected QTc was 434 ms. Episode of maximum QTc (480 ms) was in 19:00:15 during 7 minutes (in time of cooking) and an episode of the maximum duration of QTc prolongation to 477 ms was in 00:38:15 during 41 min 30 sec with heart rate - 75 beats/min.

CLINICAL SYNDROMES

Obesity, II degree. Hyperlipidemia IIa. Impaired glucose tolerance.

Syndrome of arterial hypertension with night blood pressure reduction, type «overdipper», 2 stage, 2 degree, high risk.

Syndrome of acquired QTc interval prolongation.

Syndrome of primary saphenous varicose veins in right leg.

GERD syndrome: chronic non-erosive esophagitis, remission.

Cholelithic syndrome. Chronic cholecystitis, clinical remission.

CLINICAL DIAGNOSIS

Arterial hypertension, 2 stage, 2 degree, high risk. LVMH. Syndrome of acquired QTc interval prolongation. HF 0 degree. Obesity, II degree. Hyperlipidemia IIa. Impaired glucose tolerance. Chronic cholecystitis, clinical

remission. GERD: chronic non-erosive esophagitis, remission. Primary saphenous varicose veins in right leg.

THERAPY

Ramipril 10 mg in the morning and 5 mg in the evening, atorvastatin 5 mg per day [6-7].

On the basis of the identified data changes ABPM and ECG (table 1 and 2; fig. 1a, 2a), taking into account the level of SBP night reduction: 20,6 %, «overdipper» (> 20), and DBP night reduction: 22, 1 %, «overdipper» (> 20), with insufficient reduction of blood pressure during the day, dose of ramipril in the morning was increased to 10 mg, in the evening dose was remained on 5 mg.

REPEATED EXAMINATION

Repeated examination (11.03.2015) of ABPM and ECG (table 1 and 2; fig. 1b, 2b).

During the daily monitoring, average BP level decreased from 144/85 mmHg to 136/81 mm Hg to and heart rate - from 81 to 73 beats/min. SBP value remained high for 57 % (initial value - 68 %) of the daily monitoring time, including 57 % of daytime (initial value - 80 %) and 58 % at night (initial value - 27 %), maximum HR during the day - 96 beats/min. Normal SBP during the whole period of monitoring was registered in 43 % (initial value - 31 %), 43 % in daytime (initial value - 20 %), 42 % at night (initial value - 67 %). Increasing of DBP was over 49% (initial value - 60 %) of daily monitoring time, including 41 % in daytime (initial value - 68 %) and 68% at night (initial value - 33 %). Normal DBP during the day was in 59 % (initial value - 67 %), at night - 32 % (initial value - 67 %). Degree of BP reduction at night was below normal, SBP - 9,2 % - «nondipper» (> 0 and < 10), DBP in the normal range was in 12.7 % (normal 10-20 %) on the background of ramipril 10 mg in the morning and 5 mg in the evening. Transition of SBP from «overdipper» (20,6 %) to «nondipper» (9,2 %), and DBP from «overdipper» (22,1 %) to «dipper» (12,7 %). It remains insufficient degree of BP reduction most likely due to sleep disorders (patient woke up twice at night from 01 hour 40 min to 02 h 30 min and 04 hour 10 min to 04 hour 40 min on the background of increased emotional state).

During ECG daily monitoring (11.03.2015), average HR was 72 beats/min (79 beats/min in daytime, 62 beats/min at night). Maximum HR

was 120 beats/min in the morning, minimum HR - 47 beats/min in the early morning hours (5:17:35). Circadian index was 1,27. Increasing the numbers of QTc corrected elongation episodes to 77 from 26 and average duration QTc to 442 (previous - 434) ms, QTc above normal was registered in 56 % (previous - 32 %). Increasing of maximum QTc interval prolongation and indicators with maximum period of QTc interval prolongation. Episode

with the maximum QTc interval prolongation was 496 ms with total duration - 17 minutes 30 seconds, HR in episode was 83 beats/min (previous QTc was 480 ms with total duration of 7 minutes) and episode with maximum period of QTc interval prolongation - 1 hour 18 min 00 sec with interval prolongation to 479 ms, HR in episode was 65 beats/min (1:06:15), (previous - QTc - 41 min 30 sec with interval prolongation - 477 ms (00:38:15)).

Table 1

The results of ABPM during daytime hours (07:00 - 22:00)

Indicators	Observation stages		Standards
	05.11.14	11.03.15	
Avg. SBP	151 mmHg	139 mmHg	>90 and <135
Avg. DBP	90 mmHg	82 mmHg	>60 and <85
Time index of SBP	78,2%	44,8%	<15
Time index of DBP	64,2%	26,2%	<15
VAR1 SBP	19,7 mmHg	15,1 mmHg	<15
VAR1 DBP	10,1 mmHg	12,0 mmHg	<14

Table 2

The results of ABPM during night hours (22:00 - 7:00)

Indicators	Observation stages		Standards
	05.11.14	11.03.15	
Avg. SBP	120 mmHg	127 mmHg	> 80 and <120
Avg. DBP	70 mmHg	73 mmHg	> 50 and < 70
Time index of SBP	33,7 %	47,4 %	< 15
Time index of DBP	20,9 %	31,9 %	< 15
VAR1 SBP	13,1 mmHg	13,9 mmHg	< 15
VAR1 DBP	16,7 mmHg	9,0 mmHg	< 12
Degree of nocturnal SBP reduction	20,6 % «overdipper»	9,2 % «nondipper»	> 10 and <20
Degree of nocturnal DBP reduction	22,1 % «overdipper»	12,7 % «dipper»	> 10 and <20

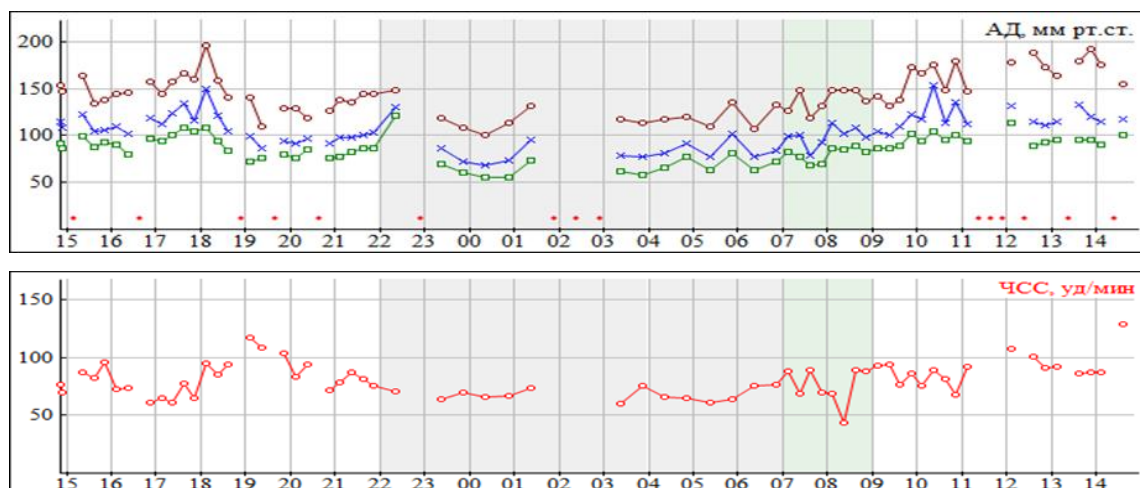


Fig.1a. Daily changes of SBP, DBP and HR (05/11/2014)

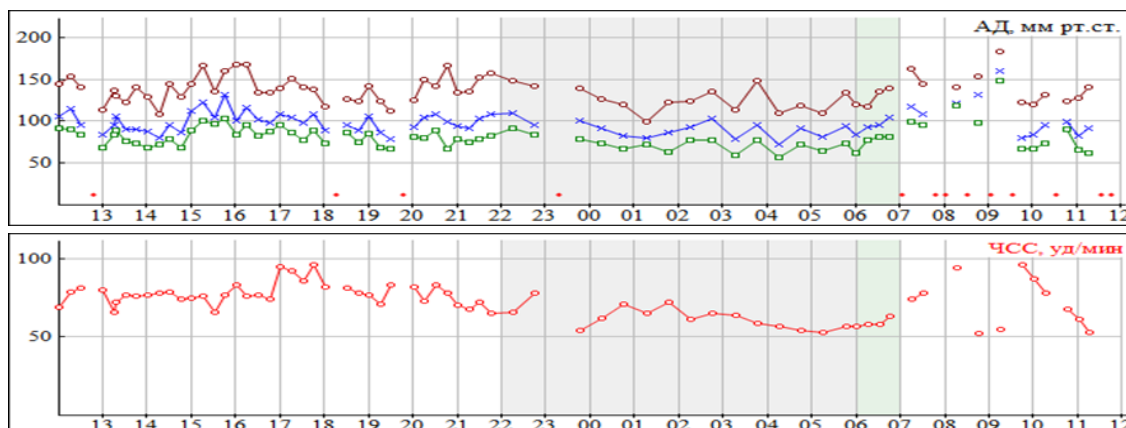


Fig.1b. Daily changes of SBP, DBP and HR 10.03.2015

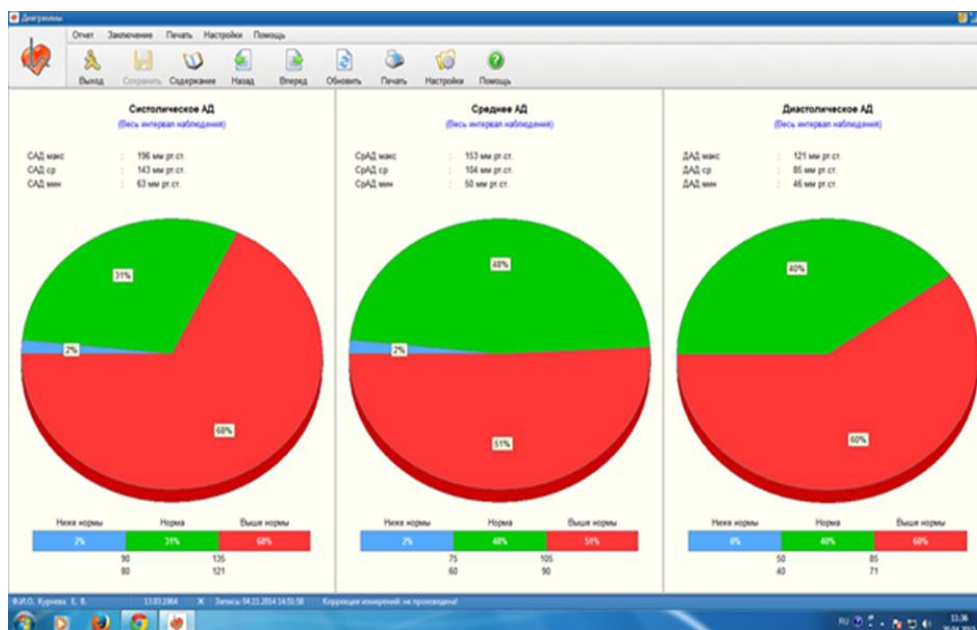


Fig.2a. Circadian profile of BP (05/11/2014)

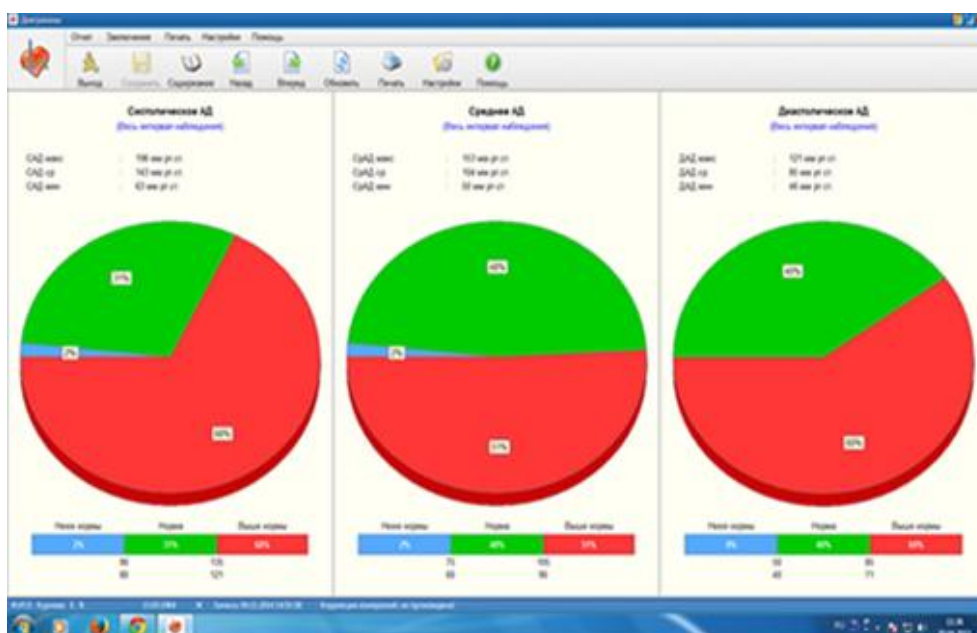


Fig.2b. Circadian profile of BP (10/03/2015)

Lipid profile has been improved during the second investigation (table 3).

Against the background of therapy in 3 months average daily SBP reduction from 143 mmHg to 136 mmHg and average daily DBP reduction from 85 mmHg to 81 mmHg was observed. Normalization of average DBP daily profile from «overdipper» to «dipper». At the same time, however, increasing the number of QTc corrected interval prolongation

episodes to 77 from 26 and increasing the proportion of elongated QTc corrected interval to 56 % against – 32 %, and conversion of the average SBP daily profile from «overdipper» to «nondipper» was detected. This condition contributes to the development of acute cardiovascular events, and therefore requires correction therapy. Our changes: ramipril 5 mg in the morning and 5 mg at night, melatonin 3 mg 30 minutes before bedtime.

Table 3

Indices of lipid spectrum

Indices	Results 24.10.14	Results 12.02.15	Norm (in SI units)
Total cholesterol	6,2	5,6	3,0 - 5,2 mmol/l - no risk 5,2 - 7,8 mmol/l – conditional risk > 7,8 mmol/l – high risk
Triglycerides	1,34	1,79	< 2,3 mmol/l
HDL	1,18	1,91	> 1,68 mmol/l - no risk 1,15 – 1,68 mmol/l – conditional risk < 1,15 mmol/l – high risk
LDL	4,73	2,67	< 2,59 mmol/l - no risk 2,59 – 4,12 mmol/l – conditional risk > 4,14 mmol/l – high risk
VLDL	0,28	0,98	0,26 – 1,00 mmol/l
Atherogenic ratio	4,2	1,9	< 3,0

Nearest goal is to restore physiological daily periodical of BP with shortening of QTc corrected interval and absolute improving patient's quality of life.

We hope that the recent intervention in the treatment regimen will lead to the expected result.

PROSPECTS FOR FUTURE STUDIES

It is interesting to re-evaluate studied parameters after 3 months on the background of therapy correction.

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Review

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CHRONOTHERAPY OF HYPERTENSION: LITERATURE REVIEW

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Review devoted to chronotherapy of hypertension. The questions of chronomedicine and chronobiology, biological rhythms, especially circadian regulation of blood pressure, types of daily blood pressure profile violations, the role of de-synchronization of biological rhythms in the development and course hypertension, opportunities to optimize antihypertensive therapy with the method of chronotherapy using alpha- and beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, diuretics, calcium channel blockers and melatonin are contemplated.

KEY WORDS: hypertension, circadian rhythms, chronotherapy, ambulatory blood pressure monitoring

ХРОНОТЕРАПІЯ ГІПЕРТОНІЧНОЇ ХВОРОБИ: ОГЛЯД ЛІТЕРАТУРИ

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Огляд присвячений хронотерапії гіпертонічної хвороби. Розглядаються питання хронобіології і хрономедицини, біологічних ритмів, насамперед, циркадної регуляції артеріального тиску, типів порушень добового профілю артеріального тиску, роль десинхронізації біологічних ритмів в розвитку і перебігу гіпертонічної хвороби, можливості оптимізації антигіпертензивної терапії методом хронотерапії з використанням альфа- і бета-блокаторів, інгібіторів ангіотензинперетворюючого ферменту, блокаторів рецепторів ангіотензину II, діуретиків, блокаторів кальцевих каналів та мелатоніну. Робиться висновок про актуальність проблеми і недостатність її розробленості.

КЛЮЧОВІ СЛОВА: гіпертонічна хвороба, циркадні ритми, хронотерапія, добове моніторування артеріального тиску

ХРОНОТЕРАПИЯ ГИПЕРТОНИЧЕСКОЙ БОЛЕЗНИ: ОБЗОР

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Обзор посвящён хронотерапии гипертонической болезни. Рассматриваются вопросы хронобиологии и хрономедицины, биологических ритмов, прежде всего, циркадной регуляции артериального давления, типов нарушений суточного профиля артериального давления, роль десинхронизации биологических ритмов в развитии и течении гипертонической болезни, возможности оптимизации антигипертензивной терапии методом хронотерапии с использованием альфа- и бета-блокаторов, ингибиторов ангиотензинпревращающего фермента, блокаторов рецепторов ангиотензина II, диуретиков и блокаторов кальцевых каналов и мелатонина. Делается вывод об актуальности и малой разработанности проблемы.

КЛЮЧЕВЫЕ СЛОВА: гипертоническая болезнь, циркадные ритмы, хронотерапия, суточное мониторирование артериального давления

Arterial hypertension (AH) is one of the most worldwide pathologies. Its prevalence in Europe is about 45 % of the general population, and characterized by dramatic increase with aging [1, 2]. Experts from the World Health Organization consider

hypertension as a scaled non-infectious pandemic [3]. AH is the most important risk factor for acute myocardial infarction and cerebrovascular events, considerable cause of mortality [3, 4]. In the Seventh report of the Joint National Committee of USA on

prevention, detection, evaluation and treatment of high blood pressure (BP) stated that with BP increase on each 20/10 mmHg, starting from the level of 115/75 mm Hg, the risk of cardiovascular diseases (CVD) is doubled [5].

Despite the advances of modern science and a wide variety of antihypertensive drugs, the management of patients with AH remains one of the most actual problems in medicine [6, 7]. According to the American Heart Association, only in 64 % of patients, who take antihypertensive medications, succeed to achieve adequate BP control. [8].

Traditional treatment regimens of AH based on the concept of homeostasis, and do not take into account the biological rhythms and their influence on physiological and pathological processes in the human body. This approach often does not provide sufficient efficacy of antihypertensive therapy [9, 10] and is accompanied by the development of a number of side effects, such as internal organs hypoperfusion, humoral profile and electrolyte balance disorders [11-14].

In accordance with the definition of Society for Research on Biological Rhythms, chronobiology is the science that objective studies the biological mechanisms of temporary structures on a quantitative basis, including the rhythmic manifestation of life [15].

Chronomedicine is a separate area of chronobiology, the purpose of which is to improve the existing and develop new methods of prevention, diagnosis and effectiveness of treatment of various diseases on the basis of the human body biorhythms data. One of the objectives of chronomedicine is to identify general and specific patterns of biorhythms violation as a result of pathological processes and develop ways of their correction.

Chronotherapy is one of the main and most developed parts of chronomedicine, and its main task is the development of methods to influence the disease process, taking into account the individual chronobiological characteristics of the patient.

A man's life from birth to death is subordinated to biological rhythms. All processes in the body, starting with the cell cycle, are oscillatory in nature with regular repetition of the same event at regular intervals of approximately equal size. [16].

Of particular interest are the circadian rhythms, which are dominant in mans life [17]. They are close in duration to the 24-hour solar day. For the first time the term «circadian rhythm» («circa» - about, «diem» - day) was first proposed by Halberg and Stephens in 1959 [18].

Many biological processes are synchronized in accordance with the periods of sleep and wakefulness, the change of day and night, the length of day photoperiod [17].

Complex self-regulating human body from birth operates on individual circadian program, the main pacemaker and synchronizer of which are suprachiasmatic nuclei (SCN) cells of the hypothalamus [19]. Exactly SCN contributes to organism adaptation to changing environmental conditions [20].

With the help of light information, coming directly from the retina, and melatonin, produced by the pineal gland, the main pacemaker monitors and synchronizes the rhythms of peripheral organs and tissues. [21].

The pineal hormone melatonin is a major endogenous regulator of biological rhythms, acting on the central circadian clock via specific melatonin receptors located in the cells of the SCN [22]. The characteristic feature is the rhythm of its secretion - melatonin is produced mainly at night, and during the day there is a decrease of its secretion [21, 22].

The role of melatonin in the regulation of diurnal BP variations is proven [23]. Melatonin stimulates the production of nitric oxide and reduces its breakup, thereby rendering a vasodilating and hypotensive action. Melatonin affects the autonomic nervous system, ensuring the dominance of its cholinergic departments on adrenergic ones. Finally, melatonin may influence BP level through their specific melatonin receptors located in the peripheral vessels and central nervous system [24].

As well as other organs and tissues, cardiovascular system has its own internal biological rhythm. Nonaka H, Takeda N, Durgan DJ, Leibetseder V proved the presence of the peripheral biological clock in the vascular endothelial cells [25], cardiomyocytes [26], vascular smooth muscle cells [27] in animals and in humans [28].

Cardiovascular system is most dynamic and its activity varies throughout the day, the seasons and years. BP, heart rate and their variability are synchronized in accordance with the periods of sleep and wakefulness [29]. The daily fluctuations in BP have a biphasic rhythm and determined by a number of internal and external factors. [30].

The internal factors include the activity of the autonomic nervous system and humoral mediators such as melatonin, cortisol, renin, vasoactive intestinal peptide, atrial natriuretic peptide, etc. [31].

External factors that determine the daily variability of BP include physical and mental activity, emotional status, food intake, state of the sleep / wake (behavioral cycle) [32].

In most healthy people there is a decrease in BP during the night and increase in daytime. In the early morning BP starts to rise, reaching a peak around 10.00 a.m. In the evening, after 19.00, it gradually decreases, reaching minimum values between 2.00 and 5.00 a.m. At night, BP in the vast majority of people is reduced by 10-20 % compared with day-time values, which is defined as the physiological degree of nocturnal decline in BP (BP ND) or dipping-pattern of circadian BP profile [33].

Circadian rhythms are quite sensitive to the action of external factors (stress, night work, change of time zone, and so on.), and their violations may be the first signs of incipient deviation in the vital activity of the organism. Desynchronization of biological rhythms leads to the violation of basic functions and the development of pathological conditions in the body [15, 34].

Desynchronizes can be defined as a pathological condition characterized by disruption of biological rhythms in the body. Desynchronizes make a significant contribution to the development of cardiovascular diseases, particularly hypertension. The presence of chronobiological disorders in hypertensive patients was noted by Pickering TG, Takeda N., Machado RM [30, 35, 36].

According to the current guidelines, the measurement of BP by Korotkoffs method remains the primary in AH diagnosis and monitoring. [2]. However, conventional single or multiple office BP measurements do not provide complete information about the daily profile of BP, as well as it is not

sufficiently informative for the AH diagnosis, for the treatment effectiveness monitoring and prognosis of cardiovascular complications [37,38].

Ambulatory BP monitoring (ABPM) is the methods which make it possible to perform the most comprehensive chronobiological analysis of the BP profile in an ordinary everyday activity of the patient.

Since the development of portable devices for ABPM at the end of the 1980s, the ABPM method was used not only in clinical studies, but clinical practice also [38]. In Canada and the UK it is recommended as the preferred method for the diagnosis of AH [39].

In patients with AH data, obtained by ABPM, most accurately reflect the severity of the disease and risk of cardiovascular events [40]. Several independent prospective studies have shown that the level of BP during sleep is the best predictor of CVD risk and target organ damage than the daily or 24-hours means of BP levels [41].

ABPM provides not only static, but also dynamic information about the level of BP. It allows, first of all, to assess the biphasic BP pattern according to the degree of its night-time reduction, the so-called «sleep-time relative BP decline», which is defined as the percent decrease in mean BP during nighttime sleep relative to the mean BP during daytime activity, and calculated as $(100 \times [\text{awake BP mean} - \text{asleep BP mean}] / \text{awake BP mean})$ [42].

Depending on the value of this present ration the following types of daily BP pattern are distinguished [42, 43]: «dippers» - physiological decrease in BP during the night - sleep-time relative BP decline 10-20 % ; «overdippers» - an excessive fall in BP at night, sleep-time relative BP decline > 20 % ; «nondippers» - the lack of BP reduction at night, sleep-time relative BP decline < 10 % ; «night-peakers» - night-time BP more than during daily activity, sleep-time relative BP decline < 0.

Sleep-time relative BP decline can be calculated for systolic (SBP), diastolic (DBP), pulse pressure and mean (MAP) arterial pressure. MAP is an integral indicator of the pressure throughout the cardiac cycle, and is calculated as the sum of one-third of SBP and two-thirds of DBP:

$$\text{MAP} = \frac{1}{3} \text{SBP} + \frac{2}{3} \text{DBP}$$

Which index - SBP, DBP or MAP – should be used to determine the circadian BP profile, still remains debated. Some authors have used sleep-time relative SBP decline to determine the BP pattern, in other works BP pattern was referred to a particular group if both SPB and DBP fit with the established criteria for the definite pattern. In such cases the authors did not specify to which group they included patients whose sleep-time relative decline for SBP and DBP were referred to different daily profiles, and whether such patients were excluded from the analysis. In some cases, the authors do not mention at all what index was chosen to determine dipping-status of the patient. Considering that in clinical practice there are common situations when one patient has different diurnal patterns of SBP and DBP, some researchers suggest to use the MAP to determine the circadian BP pattern [44].

Patients with insufficient and excessive sleep-time relative BP decline or persistent increased BP at night are referred to a group with impaired circadian rhythm of BP, which is a risk factor for a number of cardiovascular and cerebrovascular diseases [45].

Lack of BP decline at night is associated with a faster (compared to hypertensive with an adequate sleep-time relative BP decline) progression of target-organ damage. In nondippers left ventricular hypertrophy, myocardial infarction, heart failure, microalbuminuria, chronic renal failure, insulin resistance, and cerebrovascular disease are more frequent. [46].

ABPM method also allows to identify patients with early morning hypertension and morning BP surge (MBPS). Early morning hypertension is defined as elevated BP during the first two hours after awakening [47]. There is no consensus on the MBPS definition, most researchers use the method proposed by Kario et al. [48]. The authors suggest to calculate MBPS in two ways: the rise in BP during sleep, so called «sleep-trough MBPS», defined as the difference between the morning BP (average BP during the first 2 hours after awakening) and the lowest nocturnal BP (average BP of 3 readings - the lowest night-time reading plus the readings immediately before and after); and the rise of BP before awakening - prewaking MBPS, defined as the difference between the morning and preawakening BP

(average BP 2 hours before awakening) [48]. The pronounced MBPS and morning hypertension is closely correlated with target organ damage and the onset of cardiovascular events [49, 50].

Another important parameter determined by ABPM, is the so-called short-term BP variability from measurement to measurement. This parameter reflects the adaptive capabilities of neuro-humoral mechanisms of BP regulation under the influence of various external factors, such as emotional stress, exercise, and so on. Increased short-term BP variability reflects the violation of these regulatory mechanisms [51]. Prognostic value of short-term BP variability still remains not fully clarified. However, studies carried out both with hypertensive patients and in general population have shown a close relationship between short-term BP variability and the incidence of cardiovascular events. An analysis of 11 population-based studies involving 8938 patients showed that short-term BP variability from measurement to measurement is an independent factor of cardiovascular risk [52].

As circadian rhythms play an important role in the regulation of BP, AH can be defined as circadian disorder, when chronotherapeutic approach is required. Nevertheless, the data reflecting the incidence of cardiovascular disease and other complications in patients with hypertension, depending on BP pattern, in the literature is extremely small.

With the introduction of ABPM in clinical practice the ability and quality of care of patients with hypertension is increased.

Along with the maintenance of BP during the 24 hours at target level, the need to control its morning surge and to save daily BP pattern with the physiological sleep-time decline is proven [40, 53, 54]. The approach to antihypertensive therapy should be individualized according to the patient chronotype. Excessive reduction of BP with medications can lead to negative consequences such as hypoperfusion of the internal organs, pronounced MBPS, impaired physiological circadian rhythm of BP with increased risk of cardiovascular events [55, 56].

A wide range of endogenous circadian rhythms in combination with various

exogenous factors influence not only on the BP variability and its circadian pattern, but also on the pharmacokinetics and pharmacodynamics of antihypertensive drugs [57].

Studies that have examined the benefits of chronotherapy in AH, revealed clinically significant differences in the efficacy and safety of antihypertensive drugs, depending on the time of their admission - in the morning or in the evening.

Thus, in non-dippers physiological degree of sleep-time relative BP decline can be achieved through the taking antihypertensive drugs in the evening, at bedtime [58].

The effectiveness of AH treatment with beta-blockers (BB) is directly dependent on the activity of the sympathetic nervous system (SNS) [59]. BB are mostly reduced daytime BP and have little influence on his daily profile. They are more pronounced effect on the daytime BP than the nighttime reflects the circadian rhythm of the sympathetic nervous system [60].

Data on AH chronotherapy with BB are extremely small. In a study with participation 82 hypertensive patients with AH of 1-2 stage, who took nebivolol, the degree of daily BP reduction did not differ between the groups of the evening and morning ingestion of the drug [61], though a more marked reduction in the daily readings compared with the nighttime were noted, the most pronounced in the group of morning ingestion. At the same time, use of the nebivolol in the morning, along with a decrease in daily BP average, resulted in a twofold increase in the number of non-dippers, while an evening ingestion didn't have a significant influence on circadian BP profile and didn't lead to increase number of non-dippers. According to the authors' opinion, the ingestion of nebivolol in the evening is the most optimal, compared with the morning regime of drug intake, because this provides the control of BP within 24 hours, and prevents distortion of circadian BP pattern.

M.C. Acelajado et al. [62] carried out a study with participation of 38 patients with AH. 13 of them were dippers and 6 - night-pickers, all patients were randomized to groups of morning and evening nebivolol ingestion. After 3 weeks of treatment, it was found clinically significant and equivalent reduction in daytime, nighttime and 24-hours

BP means in both groups, as well as the prevalence of dipping-status in the group of patients taking the drug in the morning. In both groups there was a clinically significant effect of nebivolol on the MBPS, more pronounced in the group of the evening ingestion. The conclusion was that the effectiveness of nebivolol in reducing daytime, nighttime and 24-hours BP regardless of the time of it ingestion.

The level of BP at night is more dependent on the activity of the renin-angiotensin-aldosterone system (RAAS), so drugs that have influence on it, consider being more effective when taken at bedtime [63]. Also it should be noted that most angiotensin-converting enzyme (ACE) inhibitors are activated in the liver by process of deesterification, wherein the flow velocity during sleep is reduced, which may lead to delayed activation.

In recent decades, a number of studies on the comparative effectiveness of drugs from the group of ACE inhibitors, depending on the time of drug taking, were performed [64]. Most of them showed a more pronounced effect of the evening ingestion on nighttime BP than on daytime, with subsequent modification of the circadian BP profile to dipping-pattern [63]. It was also noted a statistically significant reduction of MBPS in the group of evening ingestion of ACE inhibitors, compared with the morning group [65].

Studies with angiotensin II receptor blockers valsartan, telmisartan, olmesartan showed the similar results. In Hermida R.C. study in 75 % of patients, who took valsartan at bedtime, were achieved physiological degree of night BP reduction, as well as a significant increase in the number of patients with adequate control of BP during the day [66]. Similarly, the ingestion of telmisartan and olmesartan in the evening was more effective than in the morning, and showed normalization of daily BP profile with maintaining its adequate control during 24 hours [67, 68].

In chronotherapeutic studies with calcium channel blockers (CCB) the effects of morning versus evening regimen of amlodipine, cilnidipine, diltiazem, isradipine, nifedipine, nisoldipine and nitrendipine ingestion were examined [69]. Both regimens showed similar efficacy in

reducing the 24-hours BP means, but evening regimen reduced it to a greater extent, resulting in a normalization of diurnal BP pattern with a substantial leveling of MBPS. In addition, taking CCB in the evening versus the morning time was associated with better tolerability and a reduction in the incidence of edema as a side effect of CCB [70].

Limited data were found comparing administration time differences for diuretics. Ingestion of torasemide (5 mg / day) before going to bed, compared with taking the same dose on awakening, demonstrated significantly greater efficacy in reducing the average daily values of SBP and DBP, while the taking after awakening did not lead to adequate reduction of nighttime BP [69].

Chronotherapy with hydrochlorothiazide was studied in a randomized controlled trial involving 181 black patients with hypertension of 1-2 degrees. In the group of patients with an evening administration versus morning had greater reductions in SBP and DBP, but the difference was not reliable enough to confirm the benefits of the evening ingestion of hydrochlorothiazide compared with the morning. The achievement of adequate 24-hours BP control in both groups of patients also failed; although in the evening group a faster decline in left ventricular mass was noted [71].

Despite the positive obtained results, the administration of diuretics at bedtime remains debated. None of the studies looked at troublesome nocturnal diuresis and quality of sleep among the night-time group.

Some researchers believe that diuretics administration at bedtime reduces the likelihood of a physiological BP pattern achievement, as the patient throughout the night will be forced to go to the toilet [72].

On the other hand, an average dose of diuretics for AH treatment, in recalculation on hydrochlorothiazide, does not exceed 50 mg / day, and in this case hypotensive action is not achieved by diuresis but through indirect and direct vasodilatory effects of diuretics [73].

The effectiveness of alpha- blockers, as well as beta-blockers, depends of the circadian rhythm of the SNS and is characterized by a marked decrease in

peripheral resistance when taken in the early morning hours [74]. Evening dosing of alpha-blocker doxazosin reduces SBP and DBP during the day and night, but the greatest effect was observed when the drug was taken early in the morning [75].

In clinical studies of Hermida at al. in patients with AH of 1-2 stage the effects of the long-acting formulation of the α -antagonist, doxazosin, depending on the time of administration was studied. A significant decrease in asleep-BP was observed with bedtime versus morning administration. Awake- and asleep-BP were also lowered from baseline, whereas morning administration did not significantly affect these values [76].

Since melatonin plays an important role in the regulation of circadian rhythms, including BP ones, and is an important endogenous hypotensive factor [22, 23], studies on the use of exogenous melatonin in hyperensive patients with impaired circadian rhythm are of interest.

Some trials showed that administration of melatonin in addition to hypotensive agents significantly reduced nocturnal systolic and diastolic blood pressure [77]. Moreover, melatonin was demonstrated to exert meteoprotective action and thereby reduce the dependence of patients with AH on the adverse environmental factors [78].

CONCLUSION

Biological rhythms play an important role in the regulation of BP, which causes the development of chronobiological approach in the treatment of AH. ABPM is an important method in patients with hypertension for diagnosis and for monitoring the disease, although this practice is still not widespread. Therapeutic interventions based on individual BP chronostructure allow to optimize treatment and to reduce the incidence of side effects of antihypertensive drugs. The hypotensive effect of all groups of antihypertensive drugs recommended for the AH treatment, is most pronounced when taken at bedtime.

Publications, however, are fragmentary and incomplete. The widespread introduction of chronotherapeutic approach into clinical practice requires further serious scientific clinical studies.

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Lecture

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ANEMIA OF CHRONIC DISEASE

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The lecture deals with one of the commonest forms of anemia which develops secondary to systemic illnesses as an inflammatory response. Main causes, pathogenesis, clinical manifestation of anemia of chronic disease and basic approaches to its diagnostics and treatment are described.

KEY WORDS: anemia of chronic disease, etiology, clinics, diagnostics, treatment

АНЕМІЯ ХРОНІЧНИХ ЗАХВОРИУВАНЬ

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В лекції розглянуто одну з найпоширеніших форм анемії, що розвивається як запальна реакція внаслідок системних захворювань. Наведені дані про основні чинники розвитку, патогенез, клінічні прояви анемії, а також базові підходи до діагностики та лікування цього захворювання.

КЛЮЧОВІ СЛОВА: анемія хронічних захворювань, етіологія, патогенез, клініка, діагностика, лікування

АНЕМИЯ ХРОНИЧЕСКИХ ЗАБОЛЕВАНИЙ

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В лекции рассматривается одна из самых распространенных форм анемий, которая развивается как воспалительная реакция в ответ на системное заболевание. Приведены данные об основных причинах возникновения, патогенезе, клинических проявлениях анемии, а также основные подходы к диагностике и лечению этого заболевания.

КЛЮЧЕВЫЕ СЛОВА: анемия хронических заболеваний, этиология, патогенез, клиника, диагностика, лечение

DEFINITION

Anemia of chronic disease (ACD), or anemia of inflammation, is the term used to describe the hypoproliferative anemia seen in response to systemic illness or inflammation [1]. ACD is the second most common form of anemia worldwide after anemia caused by iron deficiency and the commonest type of anemia among patients with chronic diseases [1, 2].

ETIOLOGY

ACD was initially considered to be associated with inflammatory, neoplastic or infectious diseases. However, later other

diseases such as major trauma, critical illnesses, heart failure were added to possible causes of ACD [1, 2].

Main etiological causes of ACD are the following:

- Chronic and acute viral, bacterial, parasitic or fungal infections (e.g., tuberculosis, chronic fungal infections, hepatitis, osteomyelitis, HIV, pneumonia, pyelonephritis, endocarditis, cellulitis, and soft tissue infections);

- Systemic connective tissue diseases, vasculitis and autoimmune disorders (e.g., rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, scleroderma,

giant cell arteritis, inflammatory bowel disease, sarcoidosis);

- Chronic diseases (e.g., chronic kidney disease (CKD), congestive heart failure, diabetes mellitus, major thrombosis, chronic pulmonary disease);
- Malignancy (hematologic and solid tumors, e.g., lymphoma, multiple myeloma, renal cell carcinoma);
- Critical illness and major trauma;
- Chronic rejection after solid-organ transplantation [2].

EPIDEMIOLOGY

Because ACD is a result of immune system activation secondary to different causes, there are no available epidemiologic data specific for this condition. Approximately 30 % of all cases of anemia are considered to be associated with chronic disorders, including CKD [3]. The estimated prevalence of anemia in rheumatoid arthritis varies from 39 % to 53 %; over 75 % of these people are believed to have ACD [4]. About 65 % of hospitalized patients develop new cases of anemia while being in the hospital, and 57 % of them are also believed to have ACD [5].

PATHOGENESIS

As mentioned above, ACD develops as a result of immune system activation secondary to different causes. A range of underlying conditions results in release of proinflammatory cytokines, as well as activation of the reticuloendothelial system [6]. These processes have a number of implications:

- *Dysregulation of iron homeostasis* which is a hallmark of pathogenesis of ACD. This abnormality along with increased uptake and accumulation of iron within storage sites in the reticuloendothelial system result in a distraction of iron from the blood into cells of the reticuloendothelial system, following decreased availability of iron for erythroid progenitor cells, and iron-restricted erythropoiesis [2]. Acute phase protein hepcidin plays a pivotal role in the development of ACD because of its property to inhibit intestinal iron absorption. Furthermore, intensification of iron uptake by macrophages and block of iron export from macrophages primarily to the bone marrow occur simultaneously. As a result,

serum iron concentration drops (with normal total amount of iron in the organism), retarding erythropoiesis and causing anemia [7]. However, sometimes this fall in serum iron concentration can be beneficial, because it makes iron less available for microorganisms retarding their growth.

Patients with CKD have additional mechanisms of development of iron deficiency. Those who are undergoing hemodialysis may develop it as a result of significant blood loss during the procedure (loss of iron can reach more than 1,000 mg per year). Contact with dialysis fluid during hemodialysis results in breakdown of folic acid. Uremic thrombocytopeny can cause gastrointestinal bleedings [8].

- *Reduction of survival of circulating red blood cells (RBCs)* due to increased erythrophagocytosis by macrophages and damage by cytokine-generated free radicals.

- *Violation of erythropoiesis* due to inhibited differentiation and proliferation of erythroid progenitors in the bone marrow. Erythropoiesis may be additionally impaired when microorganisms involve the marrow (as in HIV, hepatitis C, and malaria) or tumor cells infiltrating marrow produce proinflammatory cytokines and free radicals that have local effect on erythroid progenitor cells [2].

- *Reduced production of erythropoietin and reduced response of erythroid cells to erythropoietin* because of downregulation of erythropoietin receptors [9]. This mechanism is of great importance in patients with CKD. Secondary hyperfunction of parathyroid gland in patients with chronic renal failure causes additional suppressive effect on erythropoiesis.

DIAGNOSTIC APPROACH

The diagnosis of ACD is based on the presence of the disease, causing anemia, with excluding of other possible causes of anemia at the same time (iron, vitamin B₁₂ or folic acid deficiency, hemolysis). *Thus, diagnosis is made primarily by laboratory findings but supported by the clinical setting.*

Clinical features. In most cases, symptoms of the underlying disease prevail over anemia, but sometimes anemic syndrome may be the first manifestation of the causative disease.

General manifestations of *anemic syndrome* include pallor, fatigue, weakness, decreased exercise tolerance, and shortness of breath with exercise and are common to all types of anemia regardless of its etiology.

Clinical manifestation of *underlying disorders* may be general less specific, which can be seen in many diseases, and specific for the given cause of ACD.

General presenting features of underlying disorders which are more but less specific include fever, night sweats, anorexia, weight loss, weakness, myalgias, or arthralgias.

Findings *specific* for each type of ACD are the following:

- *those suggesting infection*: neck stiffness; tenderness of joints, shoulder girdle, abdomen, or bones; decreased breath sounds or rales;
- *those suggesting tumor*: the presence of a mass, adenopathy, hepatomegaly, splenomegaly;
- *those suggesting autoimmune disorder*: tenderness of joints or shoulder girdle, presence of a rash.

Uncommon findings are not expected in ACD and should prompt consideration of an alternative cause for the anemia. Such findings include symptoms of bleeding (e.g., melena, hematochezia, menorrhagia, metrorrhagia), positive history of high alcohol intake or of poor nutrition, history of exposure to radiation or to drugs known to be associated with the risk of anemia.

Laboratory tests. The ACD syndrome may be defined by the following constellation laboratory test results [1, 2]:

- Mild to moderate anemia with non-severe decrease in hemoglobin (Hb) level (Hb 80 g/L to 110 g/L).

Severe anemia should prompt consideration of an alternative or coexisting cause (e.g., blood loss, iron deficiency anemia, or a primary hematologic disorder).

- Anemia is either normocytic normochromic or microcytic hypochromic.

Generally, RBC indices that are normocytic and normochromic suggest ACD of fairly recent onset. RBC indices and blood smear that are microcytic and hypochromic suggest ACD has been present some weeks or months [10, 11].

- Otherwise normal RBC morphology.
- Elevated serum ferritin (sFt).

sFt is induced in response to inflammation and in ACD, with absent iron deficiency, it is typically > 100 ng/mL, and often significantly higher, thus reflecting its dual roles in iron storage and as an acute phase reactant [12] It is generally considered a marker of iron stores. Generally, when sFt is < 30 ng/mL in an anemic patient, iron deficiency can be diagnosed. However, in many patients, a combination of iron deficiency and ACD may exist [13].

- Transferrin saturation < 15 %.

The transferrin saturation is typically 5 % to 15 % in ACD indicating that the iron supply to the erythron is limited [14].

- Total iron-binding capacity (TIBC) may be normal or reduced.

Typically < 250 micrograms/dL. If it is increased (> 400 micrograms/dL), it is suggestive of iron deficiency anemia.

- Absolute reticulocyte count is low for the degree of anemia.

Indicates underproduction by the marrow which is typical in ACD.

- Elevated C-reactive protein (CRP).

It remains a fairly nonspecific measure of inflammation which helps to confirm presence of inflammation, and therefore ACD, if cause of anemia is uncertain [14].

- Significantly elevated erythrocyte sedimentation rate (ESR).

It helps to confirm presence of inflammation, and therefore ACD, if cause of anemia is uncertain. ESR is widely used as a marker of disease activity in certain diseases that are associated with ACD (e.g., rheumatoid arthritis, polymyalgia rheumatica).

- Serum erythropoietin level is usually lower than it is expected for the given degree of anemia.

Measurement of erythropoietin levels is useful only for anemic patients with Hb < 100 g/L, since erythropoietin levels at higher Hb concentrations remain well in the normal range. Furthermore, any interpretation of an erythropoietin level in ACD with Hb < 100 g/L must take into account the degree of anemia [2]. It may also be helpful in predicting patients who will respond to erythropoietin (patients with serum erythropoietin levels < 500 milliunits/mL are more likely to respond).

Biochemically anemia of chronic disease remains a clinical diagnosis of exclusion. The key test is to rule out iron deficiency:

- Soluble transferrin receptor levels – normal in ACD, elevated in iron deficiency.
- Ratio of soluble transferrin receptor to log ferritin - low (<1) in ACD, high (>2) in iron deficiency or coexisting iron deficiency and ACD.

Other laboratory tests which may be useful in ACD:

- Serum creatinine level is useful for ruling out anemia associated with renal insufficiency, although ACD may complicate anemia that is primarily due to renal disease.
- A lactate dehydrogenase (LDH) serum level is useful for ruling out hemolysis or another bone marrow disorder (elevated LDH).
- Liver function tests are used to exclude liver disease as a cause of ACD.
- Serum B12 helps to rule out B12 deficiency.
- Serum folate is useful for ruling out folate deficiency.
- Thyroid function tests are used to exclude hypo- or hyperthyroidism that can lead to anemia.
- Bilirubin (both indirect and direct) is useful for ruling out hemolysis as the cause of the anemia.

Bone marrow biopsy. Usually performed if there is suspicion of a primary hematologic disorder (e.g., myelodysplasia or a hematologic malignancy). Also may be performed, when necessary, to determine if iron deficiency is present. In ACD results are positive for iron presence and negative for evidence of tumor, dysplasia, or other abnormalities [15].

TREATMENT

Rationale for treatment of ACD is based on two considerations: (1) anemia can be generally deleterious in itself, requiring a compensatory increase in cardiac output in order to maintain systemic oxygen delivery; (2) anemia is associated with a poorer prognosis in a variety of conditions.

Thus, moderate and severe anemia warrants correction, especially in patients older than 65 years of age, those with additional risk factors (such as coronary artery disease, pulmonary disease, or CKD), or a combination of these factors [2].

Principles of treatment of ACD:

1. When possible, treatment of the underlying disease is the best approach to solve the problem of ACD. Improvement in Hb levels has been demonstrated, for example, in patients with rheumatoid arthritis who were receiving therapy with anti-TNF antibodies [2, 16].

2. In cases in which treating of the underlying disease is not feasible, for example in patients with incurable cancers or chronic renal or cardiac failure, alternative strategies are necessary [1, 2].

3. Correction of as many contributory factors as possible is also desirable, for example correction of nutritional deficiencies [1, 17].

4. Iron supplementation is recommended in patients with ACD and concomitant absolute iron deficiency [18]. Supplemental iron is not recommended for patients with ACD with normal or high ferritin levels (> 100 ng/mL) [2, 19].

Alternative strategies of therapy include RBC transfusion and erythropoiesis-stimulating agents (ESAs).

RBC transfusion is widely used for its rapid and high efficacy. It is indicated in severe anemia (Hb < 80 g/L) or life-threatening anemia (Hb < 65 g/L), particularly when the condition is aggravated by bleeding [2]. Long-term blood transfusion therapy is not recommended in patients with cancer or CKD because of iron overload and sensitization to HLA antigens that may occur in patients before renal transplantation.

Erythropoiesis-stimulating agents (ESAs). There are five ESAs currently available: epoetin-alpha (Epoetin®, Procrit®, Eprex®), epoetin-beta (Recormon®), epoetin-omega (Epomax®), epoetin-delta (Dynepo®), and darbepoetin-alpha (Aranesp®). These agents all have the same amino-acid sequence, but glycosylation varies as a result of type- and host cell specific differences in the production process. The clinical efficacy of both epoetin-alfa and epoetin-beta is similar. Darbepoetin-alpha is an erythropoietin analogue, which has a longer half-life and potency. In Ukraine the only available erythropoietin is epoetin-alpha [20].

The basis for the usage of ESAs in the ACD is decreased erythropoietin response (the serum levels of erythropoietin is significantly lower than it must be for the

given level of Hb), decreased sensitivity of erythroid progenitors to erythropoietin, ability of treatment with erythropoietin to attenuate cytokine-mediated inhibition of erythropoiesis and to stimulate iron uptake and heme biosynthesis in erythroid progenitor cells [1, 2].

ESAs are currently approved for treatment of ACD in patients with cancer who are undergoing chemotherapy, patients with CKD, and patients with HIV infection who are undergoing myelosuppressive anti-retroviral medication [2]. The efficacy of therapy with ESAs significantly varies depending on underlying cause of ACD: from 25 % in patients with myelodysplastic syndromes up to 95 % in those with rheumatoid arthritis and CKD [21, 22].

There are some controversies regarding the target levels of Hb for patients with ACD and CKD who are undergoing treatment with ESAs. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines recommend a target level of Hb in the range of 110 to 120 g/L, and the Hb should not exceed 130 g/L [23]. These goals are associated with lower mortality and less frequent hospitalization rates. The Food and Drug Administration has approved that the target Hb levels in erythropoietin-treated patients should not exceed 120 g/L [24].

Epoetin-alpha is prescribed in wide range dose of 75 – 150 mg/kg every 1-2 weeks. The standard starting dose is 100 mg/ kg every 2 weeks. Dosing should be adjusted to reach and maintain the Hb goal of 100-120 g/L.

A rise in the Hb concentration of at least 5 g/L in 2-4 weeks of treatment indicates a positive response to therapy. In the absence of elevation in the Hb concentration within 5-8 weeks, the regimen can be intensified to daily therapy or 300 U/kg 3 times weekly. In the absence of clinically meaningful positive response in 12 weeks the treatment should be discontinued [25].

Adverse effects of ESAs. Epoetin may increase the risk of serious cardiovascular events and death when it is dosed to achieve a target Hb > 120 g/L [24].

In people with ACD caused by CKD, Hb should be monitored:

- every 2–4 weeks in the induction phase of ESA therapy
- every 1–3 months in the maintenance phase of ESA therapy

- more actively after an ESA dose adjustment [26].

Long-term treatment with ESAs has been associated with increased systemic blood pressure (BP) and occurrence of seizures; hypertension has been documented to be a common side effect of intravenous use of ESAs. The possible mechanism is an imbalance between endothelin and proendothelin that leads to hyper-responsiveness to vasoconstrictive effects of norepinephrine and hyporesponsiveness to vasodilative effects of nitric oxide. For this reason, BP should always be closely monitored in patients administered with such agents [27].

ESA resistance. The working definition of ESA resistance is the requirement for greater than 150 units/kg of ESA at least 3 times per week or the sudden development of refractoriness to a previous stable maintenance dose, such that Hb level falls below target levels [28].

The common causes of ESA resistance are:

- iron deficiency (the commonest cause). Therefore, it is imperative that iron stores are adequate during ESA treatment;
- chronic infection/inflammatory state, which is attributed to inflammatory cytokines (interleukin-1);
- hyperparathyroidism (the mechanism appears to be related to bone marrow fibrosis);
- severe malnutrition [28].

Supplemental iron is prescribed with any type of ESA because sufficient body iron stores are required to achieve and maintain the target Hb. Although oral iron tablets are easily available and are of low cost, but their effectiveness is diminished due to hepcidin mediated iron block in the intestine. Hence, intravenous iron therapy is more effective [29]. Parenteral iron has been demonstrated to enhance rates of response to therapy with erythropoietic agents in patients with cancer who are undergoing chemotherapy and in patients undergoing dialysis [2]. Supplemental iron should be administered, as needed, to maintain a transferrin saturation of 20 %, and a serum ferritin level of 100 ng/mL [30].

People with ACD caused by CKD should not have iron levels checked earlier than 1 week after receiving intravenous iron. The

length of time to monitoring of iron status is dependent on the product used and the amount of iron given. Routine monitoring of

iron stores should be at intervals of 4 weeks to 3 months [28].

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