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Clinical researches

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CLINICAL FEATURES OF PATIENTS WITH PERMANENT PACEMAKERS DEPENDING ON THE STAGE OF ARTERIAL HYPERTENSION

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The study included 131 patients (70 men and 61 women) aged 69,5 ± 11,6 years who underwent permanent pacing because of atrio-ventricular block(AV), permanent atrial fibrillation(AF) and sick sinus node syndrome(SSS) with pacing modes DDD/DDDR and VVI /VVIR as well as chronic heart failure (CHF) with cardiac resynchronization therapy (CRT-P and CRT-D). Clinical features of patients were evaluated according to the stage of arterial hypertension (AH). The results showed that all patients with implanted pacemakers had hypertension the II and III stages with their ratio 1:2.5. Stable angina, diabetes mellitus (DM), AF, heart failure (HF) II A and moderate degree of AH were associated with the II stage of AH. The III stage of AH was associated with persistent AF and postinfarction cardiosclerosis, while the frequency of occurrence moderate and severe degree of AH were the same. The high frequency of AH in patients with implanted pacemakers and their relationship with other disorders in the health of patients, requires optimization of blood pressure control.

KEY WORDS: permanent pacing, arterial hypertension

КЛІНІЧНІ ОСОБЛИВОСТІ ПАЦІЄНТІВ З ПОСТІЙНОЮ ЕЛЕКТРОКАРДІОСТИМУЛЯЦІЄЮ В ЗАЛЕЖНОСТІ ВІД СТАДІЇ АРТЕРІАЛЬНОЇ ГІПЕРТЕНЗІЇ

Дерієнко Т. А.[1], Волков Д. Є.[2]
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Обстежені 131 пацієнт (70 чоловіків і 61 жінка) у віці 69,5 ± 11,6 років, які піддалися постійної електрокардіостимуляції (ЕКС) з приводу атріо-вентрикулярної блокади, постійної форми фібриляції передсердь і синдрому слабкості синусового вузла з режимами стимуляції DDD/DDDR і VVI /VVIR, а також хронічної серцевої недостатності (ХСН) з кардіоресінхронізіруючою терапією (CRT-P і CRT-D). Клінічні ознаки пацієнтів оцінювалися в залежності від стадії артеріальної гіпертензії (АГ). Результати показали, що всі пацієнти з імплантованими ЕКС мали АГ II і III стадій з їх співвідношенням 1:2,5. АГ II стадії частіше асоціювалася зі стабільною стенокардією, СД, ФП, ХСН II А та помірним ступенем АГ, АГ III стадії - з постійною формою ФП і постінфарктним кардіосклерозом, при цьому частоти помірною та важкою ступенів АГ в них була однакова. Висока частота зустрічальності у пацієнтів з імплантованими ЕКС АГ високих стадій та їх зв'язок з іншими порушеннями в стані здоров'я пацієнтів вимагає оптимізації медикаментозного контролю АТ.

КЛЮЧОВІ СЛОВА: постійна електрокардіостимуляція, артеріальна гіпертензія

КЛИНИЧЕСКИЕ ОСОБЕННОСТИ ПАЦИЕНТОВ С ПОСТОЯННОЙ ЭЛЕКТРОКАРДИОСТИМУЛЯЦИЕЙ В ЗАВИСИМОСТИ ОТ СТАДИИ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ

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Обследованы 131 пациент (70 мужчин и 61 женщина) в возрасте 69,5 ± 11,6, которые подверглись постоянной электрокардиостимуляции (ЭКС) по поводу атрио-вентрикулярной блокады, постоянной формы фибрилляции предсердий и синдрома слабости синусового узла с режимами стимуляции DDD/DDDR и VVI/VVIR, а также хронической сердечной недостаточностью (ХСН) с кардиоресинхронизирующей терапией (CRT-P и CRT-D). Клинические признаки пациентов оценивались в зависимости от стадии артериальной гипертензии (АГ). Результаты показали, что все пациенты с имплантированными ЭКС имели АГ II и III стадий с их соотношением 1:2,5. АГ II стадии чаще ассоциировалась со стабильной стенокардией, СД, ФП, ХСН II А и умеренной степенью АГ, АГ III стадии - с постоянной формой ФП и постинфарктным кардиосклерозом, при этом частоты встречаемости умеренной и тяжелой степеней АГ в них были одинакова. Высокая частота встречаемости у пациентов с имплантированными ЭКС АГ высоких стадий и их связь с иными нарушениями в состоянии здоровья пациентов требует оптимизации медикаментозного контроля АД.

КЛЮЧЕВЫЕ СЛОВА: постоянная електрокардиостимуляция, артериальная гипертензия

INTRODUCTION

Implantation of a permanent pacemaker is effective method of treatment of resistant to medical therapy life-threatening cardiac arrhythmias and bradysystiolic arrhythmia, however, it does not eliminate the problem of patient's medical support [1-3]. Arterial hypertension (AH) is one of the most important clinical syndromes requiring patient's therapeutic support. There are publications related to changes in the dynamics of blood pressure (BP) in patients with pacemaker [4-5], and treatment of individual cases. However, we did not find works in which were studied clinical features of patients with pacemakers depending on the stage of AH.

OBJECTIVE

The aim of this work is to analyze the clinical features of patients with implanted pacemakers depending on the stage of AH.

MATERIALS AND METHODS

131 patients (70 men and 61 women) aged 69,5 ± 11,6 years who underwent permanent pacing 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». The II stage of AH was diagnosed in 92 patients, 39 –had the III stage of AH. The indications for pacemaker implantation were atrio-ventricular block (AV) – 87 people (62 %), permanent atrial fibrillation(AF) – 19 people (14 %) and sick sinus node syndrome (SSS) -34 people(24 %) with pacing modes DDD/DDDR and VVI/VVIR and dilated cardiomyopathy (DCM) – 2 people (2 %) with cardiac resynchronization therapy (CRT-P and CRT-D). In the early postimplantation period (3-5 days) medical therapy was carried out by using of angiotensin converting enzyme inhibitors, beta-blockers, calcium channel blockers, antiplatelet agents, anticoagulants of direct action. Sex (male, female), age, forms of ischemic heart disease (IHD) – postinfarction cardiosclerosis and stable angina (FC I, II, III and IV), diabetes mellitus (DM) – types I and II, AF – permanent, persistent or paroxysmal, initially identified and long-term persistent and CHF stages – I, II A, II B and III, degree of AH (1, 2 and 3) - depending on the stage of AH, were estimated. The recommendations of the Association of Cardiologists of Ukraine (2008) were used to determine the degree and stage of AH [6].

Evaluation was made of the incidence of clinical features in patients with pacemaker and AH in the early postimplantation period. The results obtained are processed after forming the database. Statistical evaluation was performed using Microsoft Excel (for parametric data: M - mean value, sd - standard deviation; for nonparametric data: absolute (n, the number) and relative (p, %) of the unit). The probability of differences between groups was determined using a parametric T -Stuydenta test. The expected result was determined by level of reliability $p < 0,05$ and $p < 0,01$

RESULTS AND DISCUSSION

The table shows the distribution of patients with permanent pacing into groups in accordance with the stage of AH.

Table

Clinical features of patients with permanent pacemakers depending on the stage of arterial hypertension

Clinical features			AH stage	
			II	**III**
The proportion of patients in the sample (% ± sP)			70 ± 4	30 ± 4
Age (M ± sd)			69,1 ± 9,9	69,5 ± 9,9
Sex (n, % ±s P)		Male	54 ± 4	51 ± 4
		Female	36 ± 4	49 ± 4
IHD (n, % ± sP)	Postinfarction cardiosclerosis		0 ± 0	67 ± 4
	Stable angina	total	54 ± 4	51 ± 4
		FC I	13 ± 3	3 ± 1
		FC II	30 ± 4	38 ± 3
		FC III	10 ± 3	10 ± 3
		FC IV	1 ± 1	0 ± 0
DM (n, % ± sP)	type	II	12 ± 3	21 ± 4
Total			34 ± 4	26 ± 4
AF (n, % ± sP)	paroxysmal and persistent		20 ± 3	10 ± 3
	permanent		14 ± 3	16 ± 3
CHF stage (n, % ± sP)	total		100 ± 0	100 ± 0
	I		27 ± 4	3 ± 1
	II A		60 ± 4	56 ± 4
	II B		13 ± 3	36 ± 4
	III		0 ± 0	5 ± 2
AH degree (n, % ± sP)	1 (mild)		13 ± 3	2 ± 1
	2 (moderate)		59 ± 4	49 ± 4
	3 (severe)		28 ± 4	49 ± 4

All patients had AH the II and III stages, dominated by the III stage of AH. The II stage of AH is more common than the III stage, less often in men then in women. The average age of patients in both groups was not significantly different.

Postinfarction cardiosclerosis predominated among the patients of the III stage of AH. Stable angina was observed in half of the patients in both groups. The frequency of occurrence IHD increased, with the growth of stable angina from the I FC to the III FC, and decreased from the III to the IV FC, while in the III FC it was the same.

DM type II occurs almost in 2 times more often in patients with AH stage III, than in patients with AH stage II. Patients with DM type I groups were absent in both.

AF with AH stage II occurred in 1,5 times more often than in the III stage. Paroxysmal and persistent forms were more often in AH stage II, and permanent was in AH stage III. First and long persistent AF was not observed.

CHF was found in all patients, wherein the II A stage was observed more often in both groups. The I stage of CHF was more often in the stage II of AH. The II A stage of CHF occurred in 3 times more often at the III stage of AH, than at the II stage. The III stage of CHF observed in 5 times more often at the III stage of AH, than at the II stage.

The majority of patients had moderate degree of AH, in both groups. Severe degree of AH occurred in 2 times more often than mild degree. At the III stage of AH, the frequency of occurrence moderate and severe stages were the same, mild degree took place only in one case.

Our data confirm the high incidence and stages of AH in patients with permanent pacemakers, [5, 7] because of this its control have a special importance. Our data about the

frequency of myocardial infarction, AH and DM in patients with implanted pacemaker indirectly corresponds [8].Other results are new.

CONCLUSIONS

1. All patients with implanted pacemaker had the II and the III stages of AH with their ratio 1:2.5.
2. Stable angina, diabetes mellitus, AF, heart failure II A and moderate degree of AH were associated with the II stage of AH. The III stage of AH was associated with persistent AF and postinfarction cardiosclerosis, while the frequency of occurrence moderate and severe AH were the same.
3. The high frequency of AH in patients with implanted pacemakers and their relationship with other disorders in the health of patients, requires optimization of blood pressure control.

PROSPECTS FOR FUTURE STUDIES

It seems appropriate to study the optimization of treatment AH in patients with permanent pacemakers.

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FUNCTIONAL CLASS OF CHRONIC HEART FAILURE AND DYNAMIC OF HEMODYNAMIC PARAMETERS IN PATIENTS WITH IMPLANTED PACEMAKERS AT THE ANNUAL STAGE OF SUPPORTIVE DRUG THERAPY

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162 patients (89 men and 73 women) aged 69 ± 10 years were observed at the annual stage of supportive drug therapy after implantation of pacemakers in DDD/DDDR, VVI/VVIR and CRT-P/CRT-D modes. Changes of hemodynamic parameters were taken in consideration according to the functional class of chronic heart failure (CHF FC). Pacemakers implantation and supportive drug therapy led to transference of patients to the lower CHF FC with more significant results in CRT-P/CRT-D mode, normalization of heart rate (HR) in all CHF FC and stimulation modes, systolic (SBP) and diastolic blood pressure (DBP) in DDD/DDDR and CRT-P/CRT-D modes, end-systolic and diastolic volumes (EDV and ESV LV), left ventricular ejection fraction (LVEF) in CHF FC II in all stimulation modes and CHF FC III in DDD/DDDR and VVI/VVIR modes and size of the left atrium (LA) in CHF FC II in all stimulation modes and CHF FC I in VVI/VVIR mode. In thickness of posterior wall and interventricular septum of the left ventricle (LV PW and IVS), the sizes of the right atrium (RA) and right ventricle (RV) significant changes in any of CHF FC were not noticed, which requires drug therapy amplification.

KEY WORDS: permanent pacing, cchronic heart failure, functional class of cchronic heart failure, hemodynamic parameters, annual stage, drug therapy

ФУНКЦІОНАЛЬНИЙ КЛАС ХРОНІЧНОЇ СЕРЦЕВОЇ НЕДОСТАТНОСТІ ТА ДИНАМІКА ГЕМОДИНАМІЧНИХ ПОКАЗНИКІВ У ПАЦІЄНТІВ З ЕЛЕКТРОКАРДІОСТИМУЛЯТОРАМИ НА РІЧНОМУ ЕТАПІ ПІДТРИМУЮЧОЇ МЕДИКАМЕНТОЗНОЇ ТЕРАПІЇ

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Спостерігали 162 пацієнта (89 чоловіків і 73 жінки) у віці 69 ± 10 років на річному етапі підтримуючої медикаментозної терапії після імплантації електрокардіостимуляторів (ЕКС) в режимах DDD/DDDR, VVI/VVIR і CRT-P/CRT-D. Враховувалися зміни гемодинамічних показників з урахуванням функціональних класів хронічної серцевої недостатності (ФК ХСН). Імплантація ЕКС і підтримуюча медикаментозна терапія приводили до переходу пацієнтів у більш низькі ФК ХСН з більш значущими результати в режимі CRT-P/CRT-D, нормалізації частоти серцевих скорочень (ЧСС) у всіх ФК ХСН і режимах стимуляції, систолічного (САТ) і діастолічного артеріального тиску (ДАТ) в режимах DDD/DDDR і CRT-P/CRT-D стимуляції, кінцевого систолічного (КСО ЛШ) і діастолічного обсягу лівого шлуночка (КДО ЛШ), фракції викиду лівого шлуночка (ФВ ЛШ) в II ФК ХСН у всіх режимах і в III ФК ХСН в режимах DDD/DDDR і VVI/VVIR і розмірів лівого передсердя (ЛП) в II ФК ХСН у всіх режимах стимуляції і в I ФК ХСН - в режимі VVI/VVIR. У товщині задньої стінки (ТЗС ЛШ) і міжшлуночкової перегородки лівого шлуночка (ТМШП ЛШ), розмірах правого передсердя (ПП) і правого шлуночка (ПШ) не спостерігалося значущих змін ні в одному з ФК ХСН, що вимагає посилення медикаментозної терапії.

КЛЮЧОВІ СЛОВА: постійна електрокардіостимуляція, хронічна серцева недостатність, функціональний клас хронічної серцевої недостатності, гемодинамічні показники, річний період, медикаментозна терапія

ФУНКЦИОНАЛЬНЫЙ КЛАСС ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ И ДИНАМИКА ГЕМОДИНАМИЧЕСКИХ ПОКАЗАТЕЛЕЙ У ПАЦИЕНТОВ С ИМПЛАНТИРОВАННЫМИ ЭЛЕКТРОКАРДИОСТИМУЛЯТОРАМИ НА ГОДОВОМ ЭТАПЕ ПОДДЕРЖИВАЮЩЕЙ МЕДИКАМЕНТОЗНОЙ ТЕРАПИИ

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Наблюдали 162 пациента (89 мужчин и 73 женщины) в возрасте 69 ± 10 лет на годовом этапе поддерживающей медикаментозной терапии после имплантации электрокардиостимуляторов (ЭКС) в режимах DDD/DDDR, VVI/VVIR и CRT-P/CRT-D. Учитывались изменения гемодинамических показателей с учетом функциональных классов хронической сердечной недостаточности (ФК ХСН). Имплантация ЭКС и поддерживающая медикаментозная терапия приводили к переходу пациентов в более низкие ФК ХСН с более значимыми результатами в режиме CRT-P/CRT-D, нормализации частоты сердечных сокращений (ЧСС) во всех ФК ХСН и режимах стимуляции, систолического (САД) и диастолического артериального давления (ДАД) в режимах DDD/DDDR и CRT-P/CRT-D стимуляции, конечного систолического (КСО ЛЖ) и диастолического объёма левого желудочка (КДО ЛЖ), фракции выброса левого желудочка (ФВ ЛЖ) во II ФК ХСН во всех режимах и в III ФК ХСН в режимах DDD/DDDR и VVI/VVIR и размеров левого предсердия (ЛП) во II ФК ХСН во всех режимах стимуляции и в I ФК ХСН - в режиме VVI/VVIR. В толщине задней стенки (ТЗС ЛЖ) и межжелудочковой перегородки левого желудочка (ТМЖП ЛЖ), размерах правого предсердия (ПП) и правого желудочка (ПЖ) не наблюдалось значимых изменений ни в одном из ФК ХСН, что требует усиления медикаментозной терапии.

КЛЮЧЕВЫЕ СЛОВА: постоянная электрокардиостимуляция, хроническая сердечная недостаточность, функциональный класс хронической сердечной недостаточности, гемодинамические показатели, годовой период, медикаментозная терапия

INTRODUCTION

Permanent pacing has proved effectiveness in improvement of quality and lifetime, morbidity and mortality reduction in patients with arrhythmias and ventricular dyssynchrony associated with chronic heart failure (CHF) [1, 2]. However, it does not cancel, but modifies supportive drug therapy.

An important factor in verification of the drug therapy effectiveness in patients with permanent pacing is hemodynamic parameters as they relate to functional class (FC) of CHF that is still not reflected in the literature.

OBJECTIVE

The aim of the study is to estimate hemodynamic parameters in CHF FC in patients with implanted pacemakers stage at the annual stage of supportive drug therapy for enhancement its effectiveness.

MATERIALS AND METHODS

162 patients (89 men and 73 women) aged 69 ± 10 years, who were subject to permanent pacing, were examined at the department of ultrasonic and instrumental diagnostics with miniinvasive interventions of SI «Zaytsev V.T. Institute of General and Urgent Surgery NAMS of Ukraine». Among the indications for pacemaker implantation were atrio - ventricular block (AV block) – 89 patients (55 %) and sick sinus node syndrome (SSNS) - 32 people (20 %) with pacing DDD/DDDR mode, permanent bradysystolic atrial fibrillation (AF) – 25 patients (15 %) with pacing VVI/VVIR mode, dilated cardio-myopathy - 16 patients (10 %) with pacing CRT-P and CRT-D modes.

Inclusion criteria were pacemakers and CHF. Exclusion criteria were the stimulation of the right or left ventricle less than 50 % over the annual period of observation and age less than 40 years.

Before implantation, in the early postoperative (3-5 days), semi-annual and annual periods after implantation, depending on the CHF FC systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), end-systolic and diastolic volumes (EDV and ESV LV), left ventricular ejection fraction (LVEF), thickness of posterior wall and interventricular septum of the left ventricle (LV PW and IVS), the size of the left atrium (LA), the size of the right atrium (RA) and the size of the right ventricle (RV) were estimated.

SBP and DBP were measured by the Korotkov's method using Microlife BP AG1-20 tonometer after 5 minutes of rest.

HR was measured using CardioLab 2000 electrocardiography.

Echocardiography was done using ultrasound Toshiba Aplio 400, Siemens Cypress and Esaote MyLab Alfa equipment. Sizes of the LA, RA, RV and LV PW and IVS were measured. Calculation of EDV and ESV LV made with the Teichholz (Teichholz L.E., 1976) [3] formula: $EDV = 7 * (EDS)^3 / (2.4 + EDS)$, $ESV = 7 * (ESS)^3 / (2.4 + ESS)$. LVEF

calculation was made with the formula EF = (EDV-ESV) / EDV * 100 %.

Hardware and drug optimization were carried out at each stage of the research. Angiotensins converting enzyme inhibitors, beta-blockers, antiplatelet agents, anticoagulants of direct action, statins, anti-arrhythmic drugs were used in the drug optimization.

Patients were divided into 4 groups - CHF FC I, II, III and IV. For CHF FC diagnosis used the recommendations of the Association of Cardiologists of Ukraine (2012) [4]. In each group of patients at each stage of the study SBP, DBP, HR, EDV and ESV LV, LVEF, LV PW and IVS statistics, the sizes of the LA, RA, RV were determined.

The obtained results were processed after forming the database. Statistical evaluation was carried out with using Microsoft Excel (for parametric data: M - mean value, sd - standard deviation; for nonparametric data: absolute (n, the number) and relative (p, %) for the unit). The accuracy of differences between groups was determined using the nonparametric U - Mann -Whitney test. The expected result was determined by level of accuracy $p < 0.05$ and $p < 0.01$.

RESULTS AND DISCUSSION

Table 1 shows the hemodynamic parameters in CHF FC groups in patients with pacemakers in DDD/DDDR mode.

Table 1

Hemodynamic parameters of patients before and after pacemakers' implantation in DDD/DDDR mode depending on CHF FC (M ± sd)

Hemodynamic parameters	CHF FC															
	FC I				FC II				FC III				FC IV			
	Before pacing	3-5 days	6 month	1 year	Before pacing	3-5 days	6 month	1 year	Before pacing	3-5 days	6 month	1 year	Before pacing	3-5 days	6 month	1 year
SBP (mmHg)	149 ± 21	141 ± 11	137 ± 10	131 ± 10	150 ± 15	142 ± 19	137 ± 10	135 ± 13	153 ± 15	145 ± 18	140 ± 21	135 ± 7	162 ± 10	157 ± 15	155 ± 21	-
DBP (mmHg)	84 ± 12	84 ± 6	83 ± 5*	81 ± 7	90 ± 8	85 ± 8	85 ± 7*	81 ± 10	93 ± 7	88 ± 7	85 ± 12	85 ± 14	95 ± 6	93 ± 6	90 ± 7	-
HR (beats/ min)	47 ± 8	64 ± 9	62 ± 6	62 ± 11	45 ± 7	59 ± 19	61 ± 12	64 ± 5	46 ± 13	59 ± 17	64 ± 11	66 ± 5	44 ± 3	60 ± 7	62 ± 4	-
EDV LV (ml)	123 ± 32	117 ± 13	114 ± 18	104 ± 33	139 ± 36	135 ± 32	130 ± 28	115 ± 31	152 ± 53	146 ± 59	140 ± 28	135 ± 40	182 ± 41	161 ± 21	154 ± 42	-
ESV LV (ml)	55 ± 21	53 ± 12	51 ± 5	48 ± 7	69 ± 37	68 ± 30	63 ± 25	59 ± 25	74 ± 33	70 ± 49	68 ± 22	60 ± 19	80 ± 27	73 ± 12	69 ± 21	-
LVEF (%)	53 ± 8	51 ± 10	55 ± 3	62 ± 8	50 ±7	54 ± 10	55 ± 4	60 ± 7	46 ± 8	50 ± 5**	53 ± 3	61 ± 17	38 ± 11	41 ± 7**	47 ± 13	-
LV PW (cm)	1,2 ± 0,2	1,2 ± 0,2	1,2 ± 0,1	1,1 ± 0,2	1,2 ± 0,2	1,2 ± 0,2	1,1 ± 0,3	1,1 ± 0,2	1,3 ± 0,2	1,3 ± 0,2	1,2 ± 0,2	1,2 ± 0,2	1,3 ± 0,2	1,3 ± 0,2	1,2 ± 0,2	-
LV IVS (cm)	1,2 ± 0,2	1,2 ± 0,2	1,2 ± 0,1	1,1 ± 0,2	1,2 ± 0,2	1,2 ± 0,2	1,1 ± 0,3	1,1 ± 0,2	1,3 ± 0,2	1,3 ± 0,2	1,2 ± 0,2	1,2 ± 0,2	1,3 ± 0,2	1,3 ± 0,2	1,2 ± 0,2	-
LA (cm)	4,2 ± 1	4,2 ± 1*	4 ± 1	3,7 ± 1	4,3 ± 1	4,3 ± 1*	4 ± 1	3,8 ± 1	4,6 ± 1	4,6 ± 1	4,5 ± 1	4,3 ± 1	4,7 ± 1	4,7 ± 1	4,5 ± 1	-
RA (cm)	3,8 ± 1	3,8 ± 1	3,6 ± 0,5	3,3 ± 0,5	4,1 ± 1	4,1 ± 1	4 ± 1	3,7 ± 1	4,3 ± 1	4,3 ± 1	4,1 ± 1	3,8 ± 0,5	4,8 ± 1	4,8 ± 1	4,6 ± 1	-
RV (cm)	4,1 ± 2	4,1 ± 2	4 ± 1	3,6 ± 1	4,2 ± 1	4,2 ± 1	4,1 ± 1	3,8 ± 1	4,2 ± 1	4,2 ± 1	4,1 ± 1	3,8 ± 0,5	4,6 ± 0,5	4,6 ± 0,5	4,5 ± 0,5	-

*$p \leq 0,05$ ** $p \leq 0,01$ - in current values between the groups

Before implantation SBP was within 1 degree of arterial hypertension (AH) in CHF FC I, II, III groups and 2 degree in the CHF FC IV group. Six months after implantation there was decrease to norm in the first three groups and the tendency to decrease in CHF FC IV group. Before implantation DBP was not higher than 1 degree of AH in all CHF FC groups, but after the implantation it normalized at the early stage in the first three groups, and six months later - in CHF FC IV group.

Before implantation HR in all CHF FC groups was significantly below normal and after implantation it normalized.

EDV and ESV LV exceeded norm in CHF FC II, III, IV groups before implantation. In six months after implantation normalization noticed in CHF FC II, III groups and tendency to decrease - in CHF FC IV group. Before implantation LVEF was significantly reduced in CHF FC III, IV groups, but in six months after implantation it fully normalized in CHF FC III group and had tendency to normalization in CHF FC IV group.

LV PW and IVS exceeded the norm in all CHF FC groups before implantation. After one year implantation led to some reduction.

The size of the LA, RA and RV exceeded the norm in all CHF FC groups before implantation. A year later after implantation the size of the LA fully normalized in CHF FC I, II group, in the other groups was only tendency to reduction.

Table 2 shows the hemodynamic parameters in CHF FC groups in patients with pacemakers in VVI/VVIR mode.

Table 2

Hemodynamic parameters of patients before and after pacemakers' implantation in VVI/VVIR mode depending on CHF FC (M ± sd)

Hemodynamic parameters	CHF FC															
	FC I				FC II				FC III				FC IV			
	Before pacing	3-5 days	6 month	1 year	Before pacing	3-5 days	6 month	1 year	Before pacing	3-5 days	6 month	1 year	Before pacing	3-5 days	6 month	1 year
SBP (mmHg)	143 ± 10	138 ± 15	135 ± 17	130 ± 14	148 ± 20	144 ± 17	137 ± 14	133 ± 5	150 ± 20	145 ± 22	143 ± 7	-	160 ± 28	155 ± 21	145 ± 20	-
DBP (mmHg)	85 ± 13	82 ± 12	80 ± 12	80 ± 14**	90 ± 10	85 ± 7	86 ± 5	83 ± 5**	93 ± 8	87 ± 10**	84 ± 11	-	95 ± 7	97 ± 4**	95 ± 3	-
HR (beats/ min)	52 ± 10	64 ± 16	63 ± 5	64 ± 5**	48 ± 12	60 ± 14	62 ± 5	67 ± 3**	46 ± 13	61 ± 17	63 ± 15	-	44 ± 4	60 ± 10	60 ± 4	-
EDV LV (ml)	130 ± 47	129 ± 43	127 ± 25	122 ± 10	138 ± 32	135 ± 23	133 ± 16	124 ± 13	142 ± 37	135 ± 39	130 ± 34	-	156 ± 46	151 ± 39	148 ± 7	-
ESV LV (ml)	53 ± 29	50 ± 24	50 ± 10	48 ± 10	65 ± 36	63 ± 12	56 ± 9	53 ± 9	70 ± 36	68 ± 34	63 ± 28	-	82 ± 13	78 ± 6	72 ± 6	-
LVEF (%)	48 ± 3	51 ± 4	56 ± 9	60 ± 10	45 ± 8	49 ± 7	54 ± 7	58 ± 15	41 ± 4	47 ± 7**	51 ± 9	-	39 ± 4	43 ± 3**	47 ± 10	-
LV PW (cm)	1,2 ± 0,2	1,2 ± 0,2	1,2 ± 0,2	1,1 ± 0,2	1,2 ± 0,2	1,2 ± 0,2	1,2 ± 0,2	1,1 ± 0,5	1,3 ± 0,2	1,3 ± 0,2	1,2 ± 0,2	-	1,3 ± 0,2	1,3 ± 0,2	1,3 ± 0,1	-
LV IVS (cm)	1,2 ± 0,2	1,2 ± 0,2	1,2 ± 0,2	1,1 ± 0,2	1,2 ± 0,2	1,2 ± 0,2	1,2 ± 0,2	1,1 ± 0,5	1,3 ± 0,2	1,3 ± 0,2	1,2 ± 0,2	-	1,3 ± 0,2	1,3 ± 0,2	1,3 ± 0,1	-
LA (cm)	3,9 ± 1	3,9 ± 1	3,8 ± 1	3,6 ± 0,6	4,4 ± 1	4,4 ± 1	4,2 ± 0,5	4 ± 0,5	4,5 ± 1	4,5 ± 1	4,2 ± 1	-	4,7 ± 1	4,7 ± 1	4,4 ± 0,5	-
RA (cm)	4,1 ± 0,5	4,1 ± 0,5	4 ± 0,6	3,65 ± 0,5	4,5 ± 0,5	4,5 ± 0,5	4,3 ± 1	4,1 ± 1	4,7 ± 1	4,7 ± 1	4,5 ± 1	-	4,9 ± 0,5	4,9 ± 0,5	4,5 ± 0,5	-
RV (cm)	4,1 ± 1	4,1 ± 1	4 ± 1	3,6 ± 0,5	4,3 ± 1	4,3 ± 1	4,1 ± 1	3,9 ± 0,6	4,4 ± 1	4,4 ± 1	4,2 ± 1	-	4,6 ± 0,5	4,6 ± 0,5	4,2 ± 0,5	-

*p ≤ 0,05 ** p≤0,01 - in current values between groups

Before implantation SBP was within 1 degree of AH in the first three CHF FC groups and 2 degree in CHF FC IV group. After implantation in the early period it normalized in CHF FC I group and six months later - in CHF FC II group, in the other groups was only tendency to decrease in all observation periods.

Before implantation DBP was within 1 degree of AH in all CHF FC groups except FC I. Decrease to norm was noticed in CHF FC II, III groups by the early period of observation.

Before implantation HR was significantly below normal in all CHF FC groups, but at the early stage after implantation increased to normal.

EDV and ESV LV before implantation exceeded the norm in CHF FC II, III, IV groups. The normalization observed in CHF FC II, III groups and tendency to decrease in CHF FC IV group in six months after implantation. Before implantation LVEF was below normal in all CHF FC groups. It normalized in CHF FC I group at the early stage after implantation and after six months - in CHF FC II group.

LV PW and IVS exceeded the norm in all CHF FC groups before implantation and implanttation after one year led only to a slight decrease of the indicators.

Size LA exceeded the norm in CHF FC II, III, IV groups. Normalization was noticed only in CHF FC II group with a tendency of normalization in the other CHF FC group one year after implantation.

The size of the RA and RV was significantly higher than normal in all CHF FC groups and tendency to decrease was noticed only in a year after implantation.

Table 3 shows the hemodynamic parameters in CHF FC groups in patients with pacemakers in CRT-P/CRT-D mode.

Table 3

Hemodynamic parameters of patients before and after pacemakers' implantation in CRT-P/CRT-D mode depending on CHF FC (M ± sd)

Hemodynamic parameters	CHF FC															
	FC I				FC II				FC III				FC IV			
	Before pacing	3-5 days	6 month	1 year	Before pacing	3-5 days	6 month	1 year	Before pacing	3-5 days	6 month	1 year	Before pacing	3-5 days	6 month	1 year
SBP (mmHg)	-	-	-	-	151 ± 25	143 ± 17	138 ± 17	133 ± 6	145 ± 13	142 ± 12	140 ± 14	135 ± 7	155 ± 7	150 ± 14	140 ± 5	-
DBP (mmHg)	-	-	-	-	87 ± 14	83 ± 7	82 ± 13	83 ± 6	87 ± 7	87 ± 9	85 ± 7	85 ± 7	95 ± 7	89 ± 2	87 ± 3	-
HR (beats/ min)	-	-	-	-	56 ± 20	71 ± 13	64 ± 6	64 ± 7	58 ± 9	73 ± 7	64 ± 17	64 ± 6	58 ± 3	74 ± 17	64 ± 6	-
EDV LV (ml)	-	-	-	-	141 ± 30	137 ± 27	131 ± 42	128 ± 39	188 ± 55	181 ± 52	151 ± 22	140 ± 7	212 ± 28	195 ± 47	161 ± 6	-
ESV LV (ml)	-	-	-	-	85 ± 45	80 ± 35	61 ± 17	57 ± 8	95 ± 40	90 ± 27	68 ± 4	64 ± 7	98 ± 14	90 ± 9	83 ± 7	-
LVEF (%)	-	-	-	-	42 ± 20	47 ± 22	56 ± 8	61 ± 5	41 ± 8*	47 ± 8	48 ± 8	55 ± 6	38 ± 4	40 ± 4	44 ± 4	-
LV PW (cm)	-	-	-	-	1,3 ± 0,2	1,2 ± 0,2	1,1 ± 0,1	1 ± 0,1	1,3 ± 0,2	1,2 ± 0,2	1,2 ± 0,1	1,1 ± 0,2	1,3 ± 0,1	1,3 ± 0,2	1,2 ± 0,1	-
LV IVS (cm)	-	-	-	-	1,3 ± 0,2	1,2 ± 0,2	1,1 ± 0,1	1 ± 0,1	1,3 ± 0,2	1,2 ± 0,2	1,2 ± 0,1	1,1 ± 0,2	1,3 ± 0,1	1,3 ± 0,2	1,2 ± 0,1	-
LA (cm)	-	-	-	-	4 ± 0,9	4 ± 1	3,8 ± 0,6	3,6 ± 0,5	4,9 ± 0,7	4,8 ± 1	4,3 ± 0,8	4 ± 1	4,9 ± 0,6	4,85 ± 1	4,3 ± 0,3	-
RA (cm)	-	-	-	-	4,25 ± 0,4	4,2 ± 0,2	3,8 ± 0,6	3,5 ± 0,5	5 ± 0,5	4,9 ± 0,2	4,4 ± 0,2	4,1 ± 0,2	5,1 ± 1	5,1 ± 1	4,3 ± 0,3	-
RV (cm)	-	-	-	-	4,1 ± 0,2	4 ± 0,3*	3,6 ± 0,2	3,5 ± 0,3	4,6 ± 1	4,6 ± 0,3*	3,8 ± 0,3	3,6 ± 0,4	4,8 ± 0,1	4,8 ± 0,1	4,1 ± 0,2	-

*p ≤ 0,05 ** p≤0,01 - in current values between the groups

Before implantation SBP was within 1 degree of AH in all CHF groups, in six months after implantation it normalized in CHF FC II group and one year later - in CHF FC III one. Before implantation DBP was higher than normal in CHF FC IV group at the level 1 degree of AH and after implantation it normalized.

HR was below normal in all CHF FC groups and after implantation it increased to the norm.

Before implantation EDV and ESV LV were higher than normal, but LVEF - below normal in all CHF FC groups, but in six months after implantation it normalized in CHF FC II group, in the other groups were only the tendency to normalization.

LV PW and IVS exceeded the norm in all CHF FC groups before implantation. The slight decrease was noticed only in a year after implantation.

Before implantation LA size was higher than normal in all CHF FC groups and in six months after implantation normalization was noticed in CHF FC II group, in the other groups was the tendency to decrease. The size of the RA and RV was significantly higher than normal before implantation, but at all stages after implantation there was a tendency to the slight decrease.

Before implantation pacemakers' patients were examined in all CHF FC groups except CHF FC I one in CRT-P/CRT-D mode. One year after implantation in all stimulation modes patients' transference changed from higher to lower CHF FC, so that they disappeared in the CHF FC IV in all modes and in CHF FC III in VVI/VVIR mode.

The research has proved that at the annual stage pacemaker leads to a full HR normalization in all CHF FC groups and stimulation modes, SBP and DBP in DDD/DDDR and CRT-P/CRT-D modes, ESV LV, EDV LV, LVEF in CHF FC II group in all modes and in CHF FC III group in DDD/DDDR and VVI/VVIR modes, that confirms by the data [1, 5-8]. LV PW and IVS during the entire observation period in all stimulation modes were not changed significantly. Normalization of LA size was notice in CHF FC II group in all modes, and in CHF FC I group in VVI/VVIR mode. RA and RV sizes significantly exceeded the norm in all stimulation modes and one year later there was only a slight decrease. These results are not reflected in the literature.

Also, pacemakers' implantation led to the patients' transference from higher to lower CHF FC that was confirmed in researches [2, 5].

CONCLUSIONS

1. Supportive drug therapy of patients with implanted pacemaker at the annual stage leads to the patients' transference from higher to lower CHF FC with more significant results in CRT-P/CRT-D mode than in other stimulation modes.
2. Supportive drug therapy of patients with implanted pacemaker at the annual stage of observation leads to fully HR normalization in all CHF FC groups and stimulation modes, SBP and DBP in DDD/DDDR and CRT-P/CRT-D stimulation modes, ESV LV, EDV LV, LVEF in CHF FC II group in all modes and in CHF FC III group in DDD/DDDR and VVI/VVIR modes with the normalization of the LA size in CHF FC II group in all modes and in CHF FC I – in VVI/VVIR mode.
3. Absence of significant effect of supportive medical therapy in patients with implanted pacemaker at the annual stage on LV PW, LV IVS and sizes of RA and RV in any CHF FC do not require its amplification.

PROSPECTS FOR FUTURE STUDIES

It seems appropriate to study supportive drug therapy in patients with implanted pacemakers in different modes at the annual stage of observation depending on the CHF FC.

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SPIRONOLACTONE IN BIOFEEDBACK SESSIONS IN THE LOOP OF PACED BREATHING AND HEART RATE VARIABILITY IN HEALTHY VOLUNTEERS

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In 7 conditionally healthy volunteers, aged from 19 to 21 years (average age is 19,53 ± 1,55 years), influence of spironolactone on alterations of regulatory systems state of the organism combined with biofeedback (BFB) sessions in the loop of paced breathing (PB) and heart rate variability (HRV) parameters was evaluated. All volunteers were conducted 2 series of everyday BFB sessions in analyzed loop for 5 days with a 3 months interval between them, 2nd series of sessions were conducted 6 hours after oral application of 25 mg spironolactone. The data was analyzed using non-parametric statistical methods. Optimization of regulatory systems state under influence of BFB sessions in the loop of PB and HRV parameters was found. Spironolactone in studied dose had no significant effect on optimization of regulatory systems state.

KEY WORDS: biofeedback, paced breathing, heart rate variability, regulatory systems of the organism, spironolactone

СПІРОНОЛАКТОН В СЕАНСАХ БІОЛОГІЧНОГО ЗВОРОТНОГО ЗВ'ЯЗКУ З КОНТУРОМ МЕТРОНОМІЗОВАНОГО ДИХАННЯ ТА ВАРІАБЕЛЬНОСТІ СЕРЦЕВОГО РИТМУ У ЗДОРОВИХ ДОБРОВОЛЬЦІВ

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На 7 умовно здорових добровольцях у віці від 19 до 21 років (середній вік – 19,53 ± 1,55 років) оцінили вплив спіронолактону на якість біологічного зворотного зв'язку (БОС) в контурі метрономізованого дихання (МД) і параметрів варіабельності серцевого ритму (ВСР). Всім добровольцям проведено по 2 серії щоденних сеансів БОС у досліджуваному контурі протягом 5 днів з інтервалом у три місяці між ними, у 2-й серії сеанси проводили через 6 годин після перорального прийому 25 мг спіронолоктона. Дані оброблялися методами непараметричної статистики. Встановлена оптимізація стану регуляторних систем під впливом БОС з контуром МД і ВСР. Спіронолактон в дослідженій дозі не робив істотного впливу на якість оптимізації регуляторних систем.

КЛЮЧОВІ СЛОВА: біологічний зворотний зв'язок, метрономізоване дихання, варіабельність серцевого ритму, регуляторні системи організму, спіронолактон

СПИРОНОЛАКТОН В СЕАНСАХ БИОЛОГИЧЕСКОЙ ОБРАТНОЙ СВЯЗИ С КОНТУРОМ МЕТРОНОМИЗИРОВАННОГО ДЫХАНИЯ И ВАРИАБЕЛЬНОСТИ СЕРДЕЧНОГО РИТМА У ЗДОРОВЫХ ДОБРОВОЛЬЦЕВ

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На 7 условно здоровых добровольцах в возрасте от 19 до 21 года (средний возраст – 19,53 ± 1,55 лет) оценили влияние спиронолактона на качество биологической обратной связи (БОС) в контуре метрономизированного дыхания (МД) и параметров вариабельности сердечного ритма (ВСР). Всем испытуемым проведено по 2 серии ежедневных сеансов БОС в исследуемом контуре в течение 5 дней с временным интервалом в три месяца между ними, во 2-й серии сеансы проводили через 6 часов после перорального приёма 25 мг спиронолоктона. Данные обрабатывались методами непараметрической статистики. Установлена оптимизация состояния регуляторных систем под

влиянием БОС с контуром МД и ВСР. Спиронолактон в изученной дозе не оказывал существенного влияния на качество оптимизации регуляторных систем.

КЛЮЧЕВЫЕ СЛОВА: биологическая обратная связь, метрономизированное дыхание, вариабельность сердечного ритма, регуляторные системы организма, спиронолактон

INTRODUCTION

The function of human circulatory system is controlled by neurohumoral regulatory systems [1]. Chronic distress cause its overstrain, which forms the base for development and manifestation of diseases [2].

One of perspective ways of optimization of regulatory systems state is biofeedback in the loop of paced breathing and heart rate variability (HRV) parameters [3-6].

Spironolactone, a competitive aldosterone antagonist, inhibits aldosterone-regulated exchange of sodium to potassium ions at collective tubules and distal canaliculi of nephron, providing moderate diuretic and mild antihypertensive effects [7].

Considering the above, it is interesting to evaluate spironolactone influence on the organism in combination with biofeedback sessions in the loop of paced breathing and HRV parameters at one contingent of volunteers.

The study is conducted as a part of research project of V.N. Karazin Kharkiv National University «Development and Research of Automatic Control of Heart Rate Variability», registration No. 0109U000622.

OBJECTIVE

To evaluate spironolactone influences on alterations of regulatory systems state of the organism in combination with biofeedback sessions in the loop of paced breathing and HRV parameters at one contingent of volunteers.

MATERIALS AND METHODS

The study involved 7 conventionally healthy volunteers aged from 19 to 21 years (average age is $19{,}53 \pm 1{,}55$). Inclusion criteria: acute and chronic diseases absence, pernicious habits absence, heart rate above 60 bpm at rest, blood pressure above 100/60 mmHg.

Biofeedback sessions were conducted using computer diagnostic complex «CardioLab 2009» («KhAI-Medica») with special «Biofeedback» module that contains programmatically connected aural-visual breathing metronome and algorithm of HRV parameters estimation.

In compliance with research objective, volunteers were conducted 2 series of everyday biofeedback sessions in studied loop for 5 days with a 3 months interval between them [8]. Second biofeedback series were conducted 6 hours after oral intake of 25 mg spironolactone. Before second biofeedback series all volunteers took similar dose of spironolactone for 2 days to reach significant pharmacological effect [7].

During biofeedback session, initialization of adaptation algorithm of biofeedback module was conducted in first 2 minutes, while volunteer breathed 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 consisted in automatic seeking of such frequency, when current sympathovagal and neurohumoral values were maximally approximate to optimum zone [5].

Regulatory systems state was estimated based on HRV parameters. 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 during 7-minute biofeedback session [4]. Powerfulness of very low (VLF, ms^2), low (LF, ms^2) and high (HF, ms^2) frequencies of HRV domain spectrum were estimated, then they were transformed into two-dimensional coordinate space with LF/HF and VLF/(LF+HF) axes, which correspond to powerfulness of sympathovagal and neurohumoral balances of regulation [9].

Biofeedback quality estimation was based on 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) parameters both for whole regulatory system (D) and its parts, and also on BQI integral index (parameter that reflects all qualitative changes of biofeedback process) [9]. Estimation of all values was carried out using PTC MathCad software.

Statistical analysis of the results for each subject was carried out using Microsoft Excel. Average values (M) and standard deviation (sd) of O, S, E parameters for D, LF/HF, VLF/(LF+HF) indicators of all records of each series of all subjects were put down in spreadsheet. The differences reliability of each parameter between sessions and in each session was determined by Wilcoxon signed-rank test.

RESULTS AND DISCUSSION

O, S, E parameters values for D, L/H, V/(L+H) indicators of 1st and 5th sessions of 1st and 2nd biofeedback series in conventionally healthy volunteers are shown in the table. According to the data, biofeedback series in the loop of paced breathing under HRV parameters control optimize regulatory systems state. However, adding spironolactone to biofeedback series has no significant influence on alterations of O, S, E parameters values for D, LF/HF, VLF/(LF+HF) indicators.

Table

O, S, E parameters values for D, LF/HF, VLF/(LF+HF) indicators of 1st and 5th sessions of 1st and 2nd biofeedback series

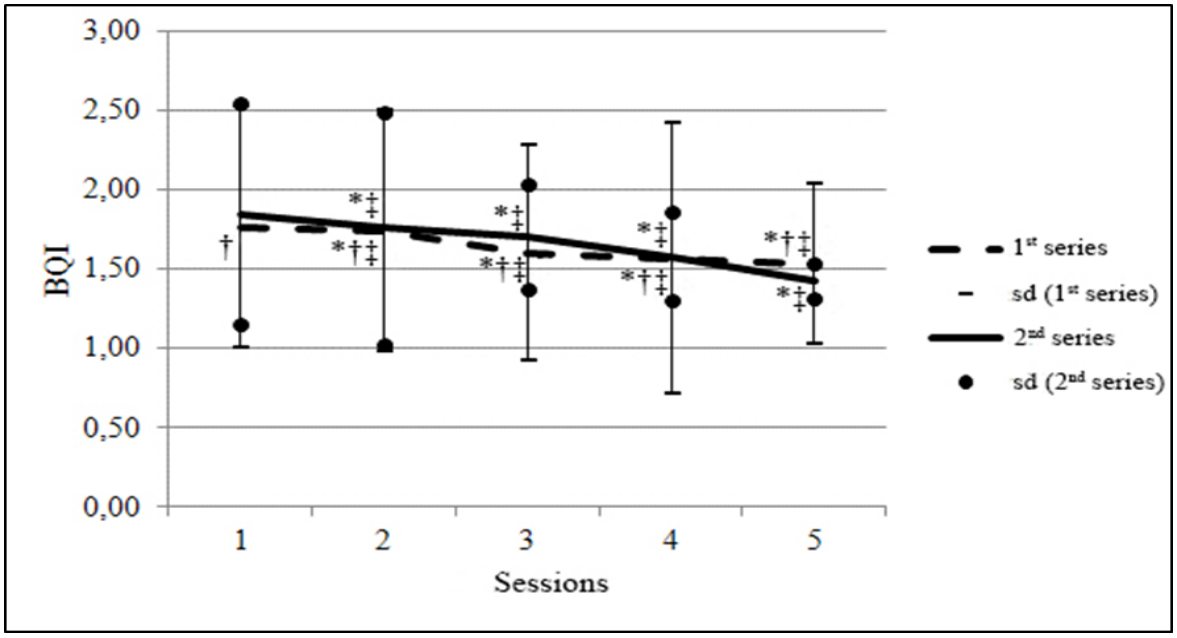
Parameters		1st series		2nd series	
		1st session	5th session	1st session	5th session
D	O	-4,09±7,12	1,07±2,60 †	-1,59±2,49 *	-1,14±2,55 *†
	S	0,76±0,41	0,77±0,33 †	1,05±0,37 *	0,80±0,47 *†
	E	0,05±0,08	0,22±0,25 †	0,00±0,17 *	0,10±0,23 *†
LF/HF	O	-28,47±61,56	-3,88±8,11 †	-7,53±6,67 *	-5,57±3,89 *†
	S	4,97±1,60	5,78±1,82 †	6,62±2,75 *	6,16±0,59 *†
	E	0,82±0,40	0,98±0,02 †	0,99±0,00 *	1,00±0,01 *†
VLF/(LF+HF)	O	-2,15±1,04	-1,85±0,98 †	-5,90±2,04 *	-2,99±0,53 *†
	S	0,41±0,26	0,40±0,26 †	0,05±2,95 *	2,05±0,03 *†
	E	0,07±0,06	0,18±0,13 †	0,03±0,41 *	0,40±0,05 *†

Notes: * – p > 0,05 on same session against base series;
† – p > 0,05 on sessions against base values of one series.

BQI values alterations of 1st and 2nd biofeedback series in every volunteer are shown on the picture. Systematic biofeedback series in the loop of paced breathing and HRV parameters lead to approximation of BQI value to optimal level. Adding spironolactone to biofeedback series bring no additional alterations to BQI value.

These results show optimization of regulatory systems of the organism by conducting systematic biofeedback series that proofs the data [3-6, 8].

Absence of spironolactone influence at 25 mg dose on regulatory systems in biofeedback series should be explained by short, predominantly local effect of the drug outside system alteration of neurohumoral regulation [7].



Pic. BQI values alterations of 1st and 2nd biofeedback series in every volunteer for 5 sessions.

Notes: * – p > 0,05 on sessions against base values;
† – p > 0,05 on same session against base series;
‡ – p > 0,05 on adjacent sessions of same series.

CONCLUSIONS

1. Systematic biofeedback sessions in the loop of paced breathing under HRV parameters control optimize regulatory systems state of the organism.
2. Adding spironolactone to biofeedback series has no significant influence on optimization of regulatory systems state.
3. Spironolactone in 25 mg dose has predominantly local and short pharmacological effect.

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DAILY BLOOD PRESSURE PROFILES IN PATIENTS WITH ARTERIAL HYPERTENSION: IS IT ENOUGH TO USE SYSTOLIC BLOOD PRESSURE ONLY

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The systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse pressure (PP) daily profiles incidence was studied in 53 patients with arterial hypertension. A significant difference in the frequency of occurrence of different types of SBP, DBP and PP daily profile was revealed. In the structure of SBP daily profile «nondipper» and «dipper» types were dominated, DBP - «dipper» and «overdipper» types, PP - «night-picker» type. The conclusion about the need to evaluate not only the SBP circadian pattern, but DBP and PP also to improve the quality of arterial hypertension diagnosis, prognosis and treatment was made.

KEY WORDS: ambulatory blood pressure monitoring, systolic blood pressure, diastolic blood pressure, pulse pressure, daily blood pressure

ТИПИ ДОБОВИХ ПРОФІЛЕЙ АРТЕРІАЛЬНОГО ТИСКУ У ПАЦІЄНТІВ З ГІПЕРТОНІЧНОЮ ХВОРОБОЮ: ЧИ ДОСТАТНЬО ОБМЕЖУВАТИСЯ ЛИШЕ СИСТОЛІЧНИМ АРТЕРІАЛЬНИМ ТИСКОМ

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Вивчено частотні характеристики добових профілів систолічного артеріального тиску (САТ), діастолічного (ДАТ) та пульсового артеріального тиску (ПТ) у 53 пацієнтів з гіпертонічною хворобою (ГХ). Виявлено істотну різницю щодо частоти виявлення типів добового профілю САТ, ДАТ і ПТ. У структурі добового профілю САТ переважали типи «nondipper» і «dipper», ДАТ - «dipper» і «overdipper», ПТ - «night-picker». Зроблено висновок про необхідність оцінки не тільки добового профілю САТ, але й ДАТ та ПТ для підвищення якості діагностики, прогнозування і лікування ГХ.

КЛЮЧОВІ СЛОВА: добове моніторування артеріального тиску, систолічний артеріальний тиск, діастолічний артеріальний тиск, пульсовий тиск, добовий профіль артеріального тиску

ТИПЫ СУТОЧНЫХ ПРОФИЛЕЙ АРТЕРИАЛЬНОГО ДАВЛЕНИЯ У ПАЦИЕНТОВ С ГИПЕРТОНИЧЕСКОЙ БОЛЕЗНЬЮ: ДОСТАТОЧНО ЛИ ОГРАНИЧИВАТЬСЯ СИСТОЛИЧЕСКИМ АРТЕРИАЛЬНЫМ ДАВЛЕНИЕМ

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Изучены частотные характеристики суточных профилей систолического артериального давления (САД), диастолического (ДАД) и пульсового (ПД) артериального давления у 53 пациентов с гипертонической болезнью (ГБ). Выявлено существенное различие частот встречаемости типов суточного профиля САД, ДАД и ПД. В структуре суточного профиля САД преобладали типы «nondipper» и «dipper», ДАД - «dipper»и «overdipper», ПД – «night-picker». Сделан вывод о необходимости оценки не только суточного профиля САД, но и ДАД и ПД для повышения качества диагностики, прогнозирования и лечения ГБ.

КЛЮЧЕВЫЕ СЛОВА: суточное мониторирование артериального давления, систолическое артериальное давление, диастолическое артериальное давление, пульсовое давление, суточный профиль артериального давления

INTRODUCTION

The assessment of the daily blood pressure (BP) periodicity is an important factor in patients with arterial hypertension (AH) [1, 2]. To characterize it, in most cases, the sleep-time relative systolic blood pressure (SBP) decline is used [3]. Taking into account the different regulatory mechanisms of systolic and diastolic blood pressure (DBP), a variety of target organ damage in their combinations, as well as in relation to cardiovascular risk, there is a hypothesis that the clinical, diagnostic and prognostic value of abnormal BP pattern in patients with AH can have not only SBP, but DBP and pulse pressure (PP) also. Complex researches of circadian SBP, DBP and PP patterns clinical significance in patients with AH in the literature are absent.

OBJECTIVE

The aim of the study is to compare the frequencies of circadian SBP, DBP and PP profiles in patients with AH to develop and introduction into practice the proposals to improve the quality of AH diagnosis, prognosis and treatment.

MATERIALS AND METHODS

On the clinical base of the Kharkov city outpatient clinic № 24 53 patients with essential hypertension were examined. The study involved 22 men (42 %) and 31 women (58 %). Average age is 58 ± 10 years. The average duration of AH is 8 ± 6 years. Newly diagnosed AH – 6 patients (11 %). AH of stage I was diagnosed in 12 patients (23 %), stage II – 30 (57 %), stage III – 11 (20 %). AH of 1 grade was determined in 23 patients (43 %), grade 2 – 26 (49 %), grade 3 – 4 (8 %). Heart failure (HF) was diagnosed in the 40 cases (75 %): HF stage I – 31 (58 %), HF stage IIA – in 8 (15 %), HF stage IIB – 1 (2 %), I functional class (FC) of HF was determined in 16 patients (30 %), II FC – 22 (41 %), III FC - 2 (4 %); coronary heart disease (CHD) – 42 cases (79 %): stable angina (I-III FC) – 8 (15 %), postinfarction cardiosclerosis (PICS) – 3 (6 %), focal atherosclerotic cardiosclerosis (ACS) – 33 (62 %).

The diagnosis of AH was made according to the recommendations of the Ukraine Association of Cardiologists of (2007), the European Society of Hypertension and the European Society of Cardiology (2013), the Committee of Experts of the World Health Organization (WHO) and the International Society of Hypertension (1999), summarized and expounded in Unified clinical protocol of primary, emergency and secondary (specialized) medical care «Arterial Hypertension» (2012) [4].

The diagnosis of CHD and its functional class, as well as the diagnosis of HF and its stage and functional class was made according to the recommendations of Ukrainian Heart Association on classification, diagnosis and treatment of cardiovascular disease (2007) [5].

Exclusion criteria were secondary hypertension, hemodynamically significant valvular heart disease, cardiomyopathies of any origin, heart failure stage III, IV FC, any acute condition (infection, trauma, surgery) within the previous 3 months., chronic decompensated or acute illness, cancer, as well as any circumstances that can hinder the ambulatory blood pressure monitoring (ABPM) implementation.

To determine the daily BP profile the ABPM was performed with an automatic oscillometric device «Kardiosens» (HAI Medica, Ukraine). ABPM was performed in a patient's normal working day; the cuff was placed at the non-dominant hand. According to the international recommendations of 2013 BP recordings were obtained automatically every 15 minutes throughout a day and every 30 minutes at night [3]. Patients should keep their habitual routine and present a report with the activities done; SBP, DBP, and PP readings were averaged for the day and the night spans according to the patients' reported time of waking up and going to bed.

All ABPM data were validated in accordance with international Ambulatory Blood Pressure Monitoring Recommendations [3], meaning exclusion the following measurements: SBP > 250 or < 70 mm Hg; DBP > 150 or < 40 mm Hg; PP > 150 or < 20 mm Hg; HR > 200 or < 20 min.

In addition, ABPM data series were considered invalid for analysis if: ≥ 30 % of the scheduled measurements were absent, BP measurement data were lacking for > 2 consecutive hourly intervals, an irregular rest-activity schedule during consecutive 24-h periods of monitoring was maintained, the nighttime sleep span was <6 h or >12 h [3].

Daily profiles of SBP, DBP and PP were classified using 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×[awake BP mean – asleep BP mean]/awake BP mean) [3].

Depending on this percent ratio, the next 24-hours patterns for SBP, DBP and PP were specified: «Dipper» - physiological decrease in BP at night, sleep-time relative BP decline 10-20 %; «Overdipper» - an excessive fall in BP at night, sleep-time relative BP decline > 20 %; «Nondipper» - the lack of BP reduction at night, sleep-time relative BP decline <10 %; «Night-peaker» - night-time BP higher than the daily one, sleep-time relative BP decline < 0 [3].

The frequency ratios of different circadian BP profiles of SBP, DBP and PP were determined and compared with each other.

Calculation of ABPM indices was performed using a computer system «Kardiosens». Statistical analysis was performed on a personal computer using the program «Microsoft Office Excel 2010» with an estimation of SBP, DBP and PP daily profile types incidence in percentage.

RESULTS AND DISCUSSION

Fig. shows the frequency ratio of SBP, DBP and PP daily profiles in the studied group of patients.

In the structure of SBP daily profile the «dipper» (42 %) and «nondipper» (47 %) types were dominant. Their frequencies of occurrence were close to each other and more than 6 times higher than the «overdipper» (6 %) and «night-picker» (6 %) incidence.

In the structure of DBP daily profile the «dipper» (34 %), «overdipper» (34 %) and «nondipper» (28 %) types were prevalent, while the «night-picker» type was extremely rare (4 %).

Due to divergent frequency ratios of diurnal profiles of SBP and DBP, in the structure of PP daily profile the incidence of «night-picker» (55 %) and «nondipper» (34 %) types was absolutely dominated, and the «dipper» (8 %) and «overdipper» (4 %) types frequency of occurrence was rare.

The obtained results have showed the different distribution of SBP, DBP and PP circadian pattern incidence in patients with AH, which is explained by the peculiarities of SBP and DBP regulation mechanisms.

Taking into account that the AH prognosis and outcomes determined by abnormal daily profile formation not only SBP [6, 7], but DBP also [8-10], as well as high frequency of occurrence «night-picker» and «nondipper» types of PP 24-hours pattern in patients with AH, revealed in our study, in clinical practice it seems appropriate to monitor the diurnal profiles of all this ABPM indices.

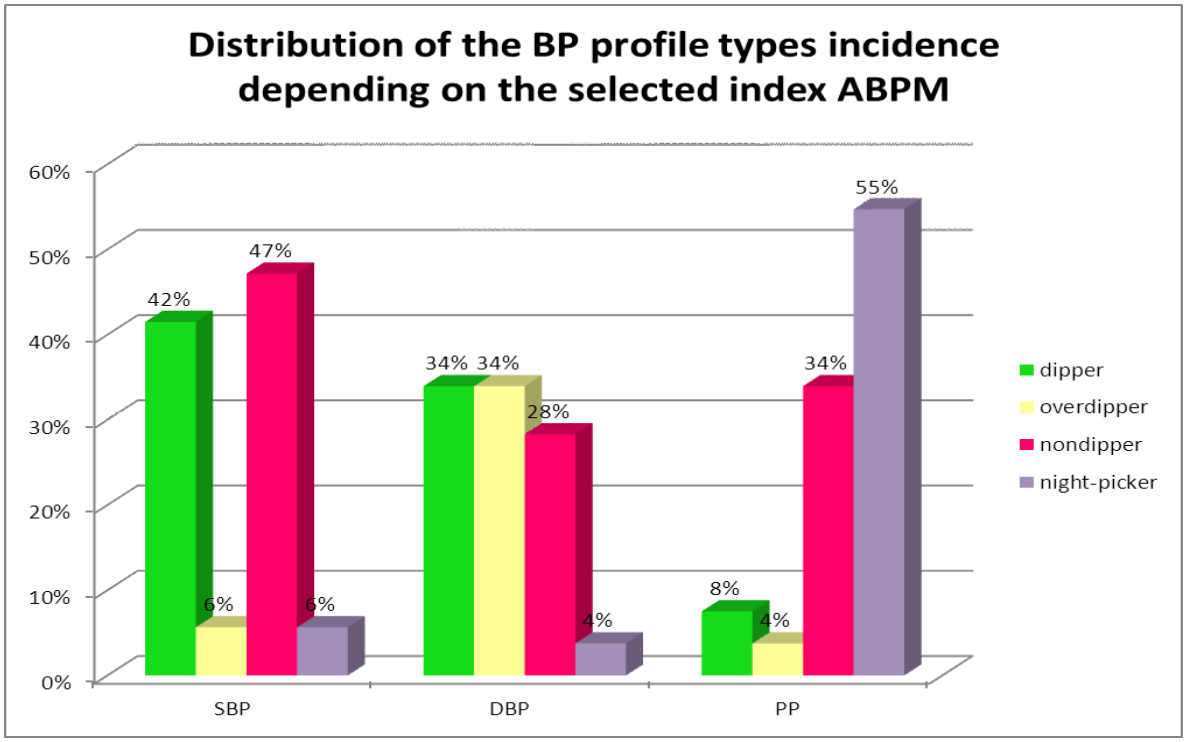

Fig. Distribution of the BP profile types incidence, depending on the selected index ABPM

CONCLUSIONS

Frequencies of occurrence distribution of SBP, DBP and PP daily profile types in patients with AH are significantly different. In the SAD daily profile structure types «nondipper» and «dipper» are dominate, DBP daily profile structure - «dipper» and «overdipper» and PP daily profile structure - «night-picker».

Different incidence ratio of SBP, DBP and PP daily profiles in patients with AH requires that in its diagnosis and prognosis the changes in each of them should be take into account.

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EFFECTS OF PERMANENT PACEMAKER ON THE PULSE PRESSURE IN PATIENTS IN EARLY POST-IMPLANTATION PERIOD

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The frequency of pulse pressure (PP) and patients migration between PP classes in 220 patients (110 men and 110 women) in average age (70 ± 9) years in the early period after pacemaker implantation (3-5 days) in VVI/VVIR, DDD/DDDR, CRT-P/D pacing modes with atrioventricular block, bundle brunch block, sick sinus node syndrome, permanent bradysystolic form of atrial fibrillation and dilated cardiomyopathy were studied. The results showed that the implantation of the pacemaker helps to normalize PP in 79 % of patients with the prevalence in class III due to reducing of PP in II, IV and V classes in the VVI, DDD, DDDR pacing mode, and there is no significant effect of it on the migration of patients in PP classes in VVIR and CRT mode. Saving in 21 % of patients II, IV and V class of PP after pacemaker implantation shows the necessity in complement drug therapy.

KEY WORDS: permanent pacemaker, arterial hypertension, pulse pressure, acute post-implantation period

ВПЛИВ ПОСТІЙНОЇ ЕЛЕКТРОКАРДІОСТИМУЛЯЦІЇ НА ПУЛЬСОВИЙ АРТЕРІАЛЬНИЙ ТИСК У ПАЦІЄНТІВ В РАННЬОМУ ПІСЛЯІМПЛАНТАЦІЙНОМУ ПЕРІОДІ

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Вивчено частоти зустрічальності пульсового артеріального тиску (ПАТ) і міграцію пацієнтів між класами ПАТ у 220 пацієнтів (110 чоловіків і 110 жінок) віком (70 ± 9) років в ранній період після імплантації електрокардіостимулятора (ЕКС) (3-5 доба) в режимах стимуляції VVI / VVIR, DDD / DDDR, CRT-P / D з атріовентрикулярною блокадою, блокадою ніжок пучка Гіса, синдромом слабкості синусового вузла, постійною брадисистолічною формою фібриляції передсердя і дилатаційною кардіоміопатією. Результати показали, що імплантація ЕКС сприяє нормалізації ПАТ у 79 % пацієнтів з концентрацією в III класі за рахунок зниження в II, IV і V класах ПАТ при VVI, DDD, DDDR режимах стимуляції, а при VVIR і CRT режимах вона не робить достовірного впливу на міграцію пацієнтів в класах ПАТ. Збереження у 21 % пацієнтів II, IV і V класів ПАТ після імплантації ЕКС показує необхідність її доповнення медикаментозною терапією.

КЛЮЧОВІ СЛОВА: постійна електрокардіостимуляція, артеріальна гіпертензія, пульсовий артеріальний тиск, гострий післяімплантаційний період

ВЛИЯНИЕ ПОСТОЯННОЙ ЭЛЕКТРОКАРДИОСТИМУЛЯЦИИ НА ПУЛЬСОВОЕ АРТЕРИАЛЬНОЕ ДАВЛЕНИЕ У ПАЦИЕНТОВ В РАННЕМ ПОСТИМПЛАНТАЦИОННОМ ПЕРИОДЕ

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Изучены частоты встречаемости пульсового артериального давления (ПАД) и миграция пациентов между классами ПАД у 220 пациентов (110 мужчин и 110 женщин) в возрасте (70 ± 9) лет в ранний период после имплантации электрокардиостимулятора (ЭКС) (3-5 сут) в режимах стимуляции VVI/VVIR, DDD/DDDR, CRT-P/D с атриовентрикулярной блокадой, блокадой ножек пучка Гиса,

синдромом слабости синусового узла, постоянной брадисистолической формой фибрилляции предсердия и дилатационной кардиомиопатией. Результаты показали, что имплантация ЭКС способствует нормализации ПАД у 79 % пациентов с концентрацией в III классе за счет снижения во II, IV и V классах ПАД при VVI, DDD, DDDR режимах стимуляции, а при VVIR и CRT режимах она не оказывает достоверного влияния на миграцию пациентов в классах ПАД. Сохранение у 21 % пациентов II, IV и V классов ПАД после имплантации ЭКС показывает необходимость ее дополнения медикаментозной терапией.

КЛЮЧЕВЫЕ СЛОВА: постоянная электрокардиостимуляция, артериальная гипертензия, пульсовое артериальное давление, острый постимплантационный период

INTRODUCTION

Permanent pacemaker is the standard treatment for patients with such disorders as bradyarrhythmia and chronic heart failure (CHF) [1]. One of its positive effects is the improvement of the pumping function of the heart, what increases the blood pressure (BP) [2–4].

Pulse pressure (PP) rises when systolic blood pressure (SBP) increases, what negatively affects the hemodynamics of elastic properties of the major vessels and function of the left ventricle (LV) [5–7]. However, there is only one research, which contains PP changes in patients with a pacemaker [8] studying, but the classes of PP were not studied.

OBJECTIVE

Purpose of this study is to investigate effects of permanent pacemaker on the PP in the early post-implantation period, for developing proposals for the control of blood pressure and complement drug therapy.

MATERIALS AND METHODS

220 patients, including 110 men and 110 women were examined in the department of ultrasound and instrumental diagnostics with miniinvasive interventions of SI «V. T. Zaytsev Institute of General and Emergency Surgery NAMS of Ukraine». Mean age of the patients was 70 ± 9 years; all of them were implanted pacemaker in period from 2006 to 2015. Indications for pacemaker implantation were: atrioventricular (AV) block - 125 patients, bundle branch block - 55, sick sinus syndrome (SSS) – 51 patients, permanent bradysystolic form of atrial fibrillation (AF) - 70, dilated cardiomyopathy (DCM) – 16 patients. The patients were treated with different pacing modes: VVI / VVIR (isolated ventricular node without or with frequency adaption) – 69 patients, DDD / DDDR (double chamber pacing without or with frequency adaption) – 132 patients, CRT-P / D – 19 patients.

Exclusion criteria were: age less than 40 years, the presence of concomitant angina IV functional class (FC), chronic heart failure (CHF) IV FC.

SBP and DBP were measured by Korotkov's method according to the recommendations of the Association of Cardiologist of Ukraine for the prevention and treatment of hypertension by tonometer Microlife BP AGI-20 after 15 minutes rest. PP was calculated by the formula: PP=SBP-DBP (mm Hg).

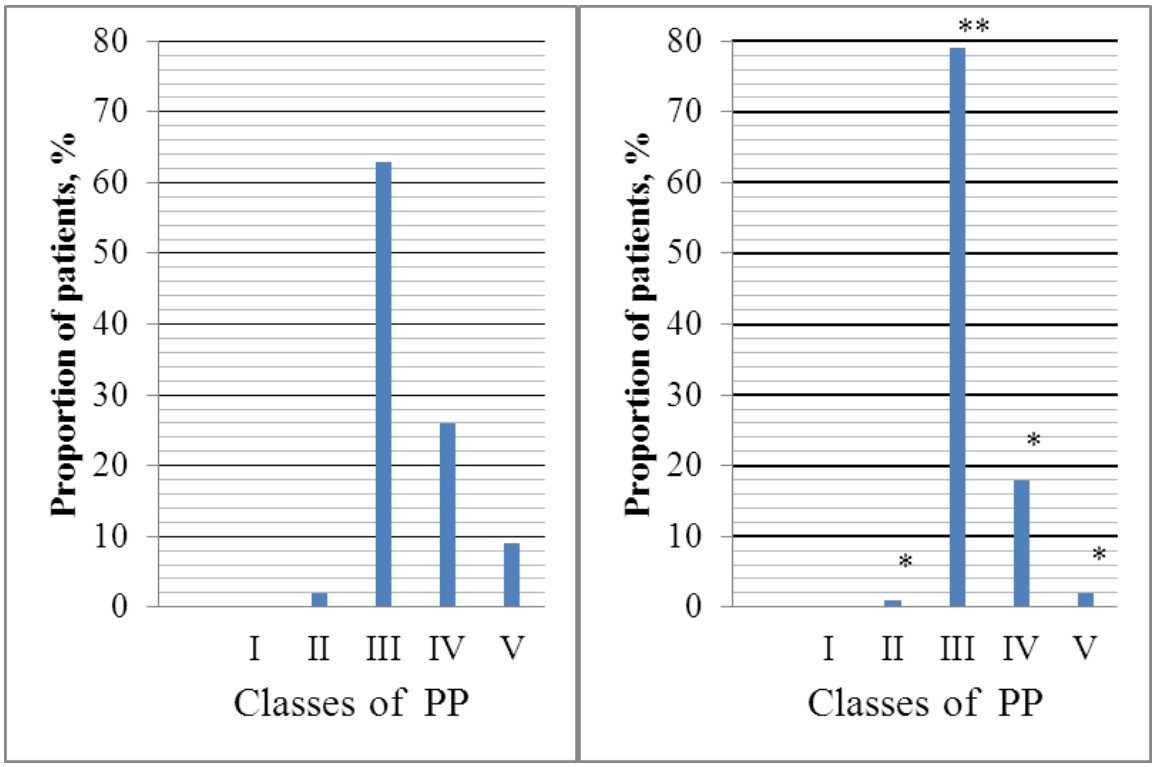
Patients were assigned into five classes according to levels of PP: I - very low PP - less than 20 mm Hg; II – low PP - from 20 to 40 mm Hg; III – normal PP - from 40 to 60 mm Hg; IV – high PP – from 60 to 80 mm Hg; V – very high PP – more than 80 mm Hg.

Frequencies of occurrence of PP and patients migration between PP classes were studied before the operation, and in the early postoperative period (3–5 days) after the pacemaker implantation at various modes of stimulation.

The data were brought into the Microsoft Excel base. For statistical evaluation of the results were used the parametric criteria (relative (p, percentage (%) and the mean percenttage error (sP)) units). Probable results were determined at levels of reliability $p < 0,05$ and $p < 0,01$.

RESULTS AND DISCUSSION

Frequencies of PP classes' occurrence in patients before and in the early period after pacemaker implantation are shown in Fig. Pacemaker implantation in the acute post-implantation period has positive effect on PP, what manifests by increasing frequency of PP class III ($p \leq 0,01$) because of reducing frequency of II, IV and V of PP classes ($p > 0,05$).



a **b**

Fig. Frequencies of PP classes' occurrence in patients before (a) and in the early period after (b) pacemaker implantation

Note: * p > 0,05; **p ≤ 0,01 - in the class between the baseline values.

Frequencies of PP classes' occurrence in patients before and in the early period after pacemaker implantation at various pacing modes are presented in Table 1. Pacemaker implantation in the acute period is presented by increasing frequency of PP class III in VVI, DDD, DDDR pacing modes (p ≤ 0,01) because of reducing frequency of II, IV and V of PP classes, and frequencies of PP classes' occurrence in VVIR and CRT pacing modes were not significantly changed.

Table 1

Frequencies of PP classes' occurrence in patients before and in the early period after pacemaker implantation at various pacing modes

		PP classes (% ± sP)							
		II		III		IV		V	
Pacing modes	All of patients in class (n, % ± sP)	Before pacing	After pacing	Before pacing	After pacing	Before pacing	After pacing	Before pacing	After pacing
VVI	55 (25 ± 3)	2 ± 1	2 ± 2	63 ± 3	78 ± 6**	26 ± 3	16 ± 5#	9 ± 2	4 ± 2#
VVIR	14 (6 ± 2)	2 ± 1	0	63 ± 3	79 ± 10*	26 ± 3	21 ± 10*	9 ± 2	0
DDD	61 (28 ± 3)	2 ± 1	2 ± 2	63 ± 3	79 ± 5**	26 ± 3	16 ± 5*	9 ± 2	3 ± 2*
DDDR	71 (32 ± 3)	2 ± 1	1 ± 1	63 ± 3	80 ± 5**	26 ± 3	17 ± 4#	9 ± 2	1 ± 1
CRT	19 (8 ± 2)	2 ± 1	0	63 ± 3	74 ± 10*	26 ± 3	26 ± 10*	9 ± 2	0

Note: *p > 0,05, **p ≤ 0,01, #p < 0,05 - in the class between the baseline values.

Results of patients' migration between PP classes in the early period after pacemaker implantation are shown in Table 2. Most of patients (16 %) after pacemaker implantation migrated from II, IV and V classes to III class of PP (79 % of patients). Only 6 % of patients with classes III and V migrated to class IV and only 0.5 % - from III to the II class of PP. Preservation of II, IV and V classes of PP was registered in 21 % of patients.

Table 2

Results of patients' migration between PP classes in the early period after pacemaker implantation

Patients (% ± sP)	PP classes			
	II	III	IV	V
Were in class	2 ± 1	63 ± 3	26 ± 3	9 ± 2
Remaining in class	1 ± 1	62 ± 3	11 ± 2	2 ± 1
Moved into class I	0	0	0	0
Moved into class II	-	0,5 ± 0,5	0	0
Moved into class III	1 ± 1	-	15 ± 2	0,5 ± 0,5
Moved into class IV	0	0,5 ± 0,5	-	6 ± 2
Moved into class V	0	0	0	-
Became in class	1 ± 1	79 ± 3	18 ± 3	2 ± 1

The received data about the improving of PP in patients in the early period after pacemaker implantation, what manifested by its concentration in class III because of reducing in II, IV and V classes of PP, broadly in line with [8] in which, however, classes of PP were not studied.

We could not find studies which have examined the migration of patients between PP classes, which occurs by theirs transfer from class III to II, IV and V classes of PP, according to the data obtained.

Concentration of patients in class III of PP, what is established in the early period after the pacemaker implantation, corresponding to its physiological values, indicates its positive influence on the course of hypertension. However, preservation of PP in non-physiological classes in some patients or their transition only to the II, IV classes from class V shows the need for additional supportive drug therapy.

CONCLUSIONS

1. Pacemaker implantation promotes the normalization of PP in 79 % of patients with concentration in class III by reducing in II, IV and V classes of PP.
2. After early period of pacemaker implantation the concentration of patients in the III class of PP occurs in VVI, DDD, DDDR pacing modes, and in VVIR and CRT pacing mode it has no significant effect on the migration of patients in PP classes.
3. Preservation of II, IV and V classes of PP in 21 % of patients after pacemaker implantation shows necessity of its complement drug therapy.

PROSPECTS FOR FUTURE STUDIES

Further investigation of effect of drug therapy on the optimization of PP in patients with implanted pacemaker in the long pacing period seems to be a perspective direction of researches.

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ROLE OF GLYCAEMIA LEVEL IN THE DEVELOPMENT OF INTERSTITIAL COLLAGEN IN PATIENTS WITH CORONARY HEART DISEASE AND TYPE 2 DIABETES

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A role of blood glucose levels in the development of interstitial collagen has been studied in 84 patients (53 women and 31 men, average age 60 ± 2.4 years) with coronary heart disease (CHD). All patients were divided into twocomparable groups: a study group including patients with coronary heart disease andtype 2 diabetes mellitus (DM) and a control group consisting of patients with coronary heart disease without DM. All patients received standard medical therapy as recommended by the European Society of Cardiology. The level of blood glucose in both groups was assessed by the standard technique, a degree of interstitial collagen volume fraction (ICVF) was measured using the formula of J. Shirani et al. The data were processed by parametric and nonparametric statistical methods. It has been proved that hyperglycemia in type 2 diabetes contributes to the development of ICVF, the degree of which increases with the rise of blood glucose level. A high level ofICVF in patients with coronary heart disease and diabetes type 2 can be a predictor of myocardial dyssynchrony development and heart failure progression, therefore, a close monitoring and timely correction of changes of blood glucose levelsare recommended to prevent the complication development. ICVF evaluation should become a routine diagnostic method in all patients with type 2 diabetes.

KEY WORDS: interstitial collagen volume fraction, type 2 diabetes mellitus, coronary heart disease

РОЛЬ РІВНЯ ГЛІКЕМІЇ У РОЗВИТКУ ІНТЕРСТИЦІАЛЬНОГО КОЛАГЕНУ У ПАЦІЄНТІВ НА ІШЕМІЧНУ ХВОРОБУ СЕРЦЯ ТА ЦУКРОВІЙ ДІАБЕТ 2-ГО ТИПУ

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На 84 пацієнтах (53 жінок і 31 чоловіків, середній вік 60 ± 2,4 років) на ішемічну хворобу серця (ІХС) вивчена роль рівня глікемії у розвитку інтерстиціального колагену. Всі пацієнти були розділені на групу спостереження, де були пацієнти з ІХС та цукровим діабетом (ЦД) 2 типу та групу контролю - пацієнти з ІХС без ЦД. Всі пацієнти отримували стандартну медикаментозну терапію відповідно до рекомендацій European Society of Cardiology. Рівень глікемії в обох групах оцінювався згідно загальноприйнятої методики, ступінь наявності об'ємної фракції інтерстиціального колагену (ОФІК) вимірювали за допомогою формули J. Shirani та співавторів. Дані обробляли методами параметричної та непараметричної статистики. Доведено, що гіперглікемія при ЦД 2 типу сприяє розвитку ОФІК, ступінь наявності якої зростає зі зростанням рівня глікемії. Високий рівень ОФІК у пацієнтів з ІХС і ЦД 2-го типу може бути предиктором розвитку диссинхроній міокарда та прогресування ХСН, тому рекомендовано ретельний контроль і своєчасна корекція рівня глікемії для попередження розвитку ускладнень. Визначення ОФІК має стати рутинним методом діагностики у всіх пацієнтів на ЦД 2-го типу.

КЛЮЧОВІ СЛОВА: об'ємна фракція інтерстиціального колагену, цукровий діабет 2-го типу, ішемічна хвороба серця

РОЛЬ УРОВНЯ ГЛИКЕМИИ В РАЗВИТИИ ИНТЕРСТИЦИАЛЬНОГО КОЛЛАГЕНА У ПАЦИЕНТОВ С ИШЕМИЧЕСКОЙ БОЛЕЗНЬЮ СЕРДЦА И САХАРНЫМ ДИАБЕТОМ 2-ГО ТИПА

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На 84пациентах (53 женщин и 31 мужчин, средний возраст 60 ± 2,4 лет) с ишемической болезнью сердца (ИБС) изучена роль уровня гликемии в развитии интерстициального коллагена. Все пациенты были разделены на сопоставимые группу наблюдения, где были пациенты с ИБС и сахарным

диабетом (СД) 2 типа и группу контроля - пациенты с ИБС без СД. Все пациенты получали стандартную медикаментозную терапию согласно рекомендациям EuropeanSocietyofCardiology. Уровень гликемии в обеих группах оценивался по общепринятой методике, степень выраженности объемной фракции интерстициального коллагена (ОФИК) измеряли с помощью формулы J. Shirani и соавторов. Данные обрабатывались методами параметрической и непараметрической статистики. Доказано, что гипергликемия при СД 2 типа способствует развитию ОФИК, степень выраженности которой возрастает с ростом уровня гликемии. Высокий уровень ОФИК у пациентов с ИБС и СД 2-го типа может быть предиктором развития диссинхроний миокарда и прогрессирования ХСН, поэтому рекомендуется требуется тщательный контроль и своевременная коррекция уровня гликемии для предупреждения развития осложнений. Определение ОФИК должно стать рутинным методом диагностики у всех пациентов с СД 2-го типа.

КЛЮЧЕВЫЕ СЛОВА: объемная фракция интерстициального коллагена, сахарный диабет 2-го типа, ишемическая болезнь сердца

INTRODUCTION

Coronary heart disease (CHD) remains the leading cause of death and disability among the working-age population. According to P. Heidenreichet al., by 2030 the prevalence of coronary heart disease will increase by 9.3 %, which will be associatedwith the direct medical cost grow by 198 % compared to year 2010 [1]. Concomitant type 2 diabetes significantly increases the severity of patient'sconditiondue to formation ofmyocardial dyssynchrony, progression of heart failure (HF) and a number of other pathological conditions [2]. The cause is hyperglycemia, which triggers the activation of the systemic immune inflammation and mediates the degradation of extracellular matrix and formation of myocardial fibrosis [2-4] with the increase of interstitial collagen volume fraction (ICVF) [5-6].

However, there are no data in the literature on the dependence of glycaemia level from the ICVF levels in patients with coronary heart disease and type 2 diabetes, which makes this study relevant.

Current work was performed according to the scientific research planof the Chair of Therapy and Nephrology of Kharkiv Medical Academy of Postgraduate Education «Cardiac and neurohumoral mechanisms of chronic heart failure in patients with concomitant diseases» (№ DR 0111U003579).

OBJECTIVE

To study the influence of glycaemia on the formation of interstitial collagen in patients with coronary heart disease and type 2 diabetes mellitus.

MATERIALS AND METHODS

57 patients (42 women (73 %), 15 men (27 %)) of average age 63 + 2.4 years were enrolled in this study. The enrollment criteriawere coronary heart disease and type 2 diabetes, chronic heart failure of I-III Functional Class according to NYHA with preserved systolic function (ejection fraction > 55 %). Patients were excluded from the analysis in case they had acute coronary disease or chronic renal failure.

The control group consisted of patients with coronary heart disease without DM – 27 participants (16 men (59 %), 11 women (41 %)) of average age 57 + 2.3 years.

The diagnosis of ischemic heart disease was established according to the recommendations of European Society of Cardiology (ESC) on the basis of anamnesis, results of clinical and laboratory examinations, specificfeatures on the ECG, echocardiography [7-8].

The diagnosis of type 2 diabetes was establishe daccording to the recommendations of American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) considering the diagnostic criteria for type 2 diabetes.

According to the recommendations of European Society of Cardiology [9-10], all patients with ischemic heart diseasewere prescribed ACE inhibitors Ramipril 10 mg, β-blocker Nebivolol 5 mg, antiplatelet Acetylsalicylic acid 75 mg, potassium-sparing diuretic Eplerenone50 mg, HMG-CoA reductase inhibitor Rosuvastatin 10 mg, and metabolic drug Trimetazidine 60 mg.

Patients with type 2 diabetes mellitus additionally received oral hypoglycemic agents: Metformin 1500 mg and Glimepiride 4 mg as a daily doseregarding the level of blood glucose. Plasma glucose levels were measured in the fasted state after an 8-14-hour

period of overnight fast. Glucose concentration in the capillary whole blood was measured by enzymatic method using standard kits.

The degree of interstitial collagen volume fraction was calculatedfrom the formula of J. Shirani et al [8]: ICVF (%) = $(1\text{-}1{,}3*\frac{totalQRS(mm)\,x\,height\,(m)}{LVMM\,(g)})*100$, wherein the normal level of ICVF was set within the range of 1 % and 2 %.

A 12-lead electrocardiogram registration was performed using the apparatus CardioLab (STC «HAI – Medica», Kharkov, Ukraine) according to the standard calculation procedures and guidelines.

LVMMI was calculated as the ratio of the left ventricular myocardial mass (LVMM) to body surface area, the LVMM was evaluated using the echocardiography (Echo-CG) on the following equipment: Siemens Ac USONSC 2000 (Siemens Medical Solution, Mountain View, USA) and ULTIMA PRO-30 («Radmir», Ukraine) applying a 3.5 MHz-probe with synchronous ECG registration in four cardiac cycles from the standard approaches in accordance with conventional procedure described in the guidelines of American Society of Echocardiography.

After database formation the data were processed using Microsoft Excel and program «Statistica». Parametric (M, sd) and non-parametric (absolute and relative - proportions (p, %) and criterion χ^2) criteria were used for statistical evaluation of the results. The chance of differences between groups was calculated by nonparametric Mann-Whitney U-test criterion. The expected result was evaluated by the confidence level $p < 0.01$ and $p < 0.05$.

RESULTS AND DISCUSSION

The figure shows the dependence of the degree of ICVF from blood glucose levels in patients with coronary heart disease.

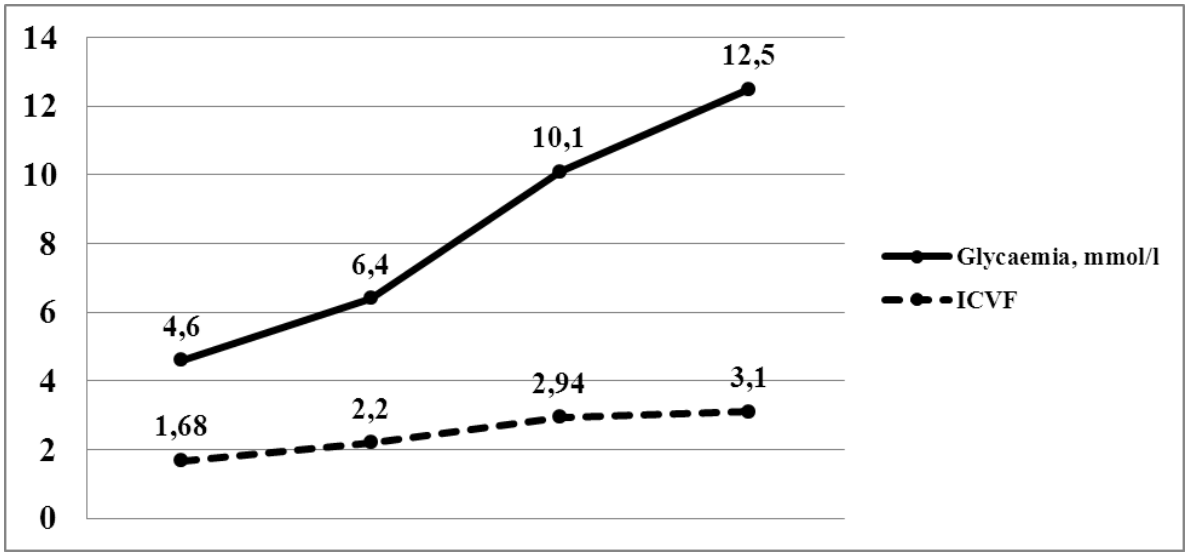

Fig. The effect of glycaemia on the level of ICVF in both groups of patients

In patients with a glucose concentration of 4.6 ± 1.2 mmol/l in the capillary whole blood in fasted state, a ICVF level remained within normal limits (1,68 ± 0.3 %), while the increase of glucose concentration to 6.4 ± 1,3 mmol/l was associated with ICVF level elevation to 2.2 + 0.51 %. At the blood glucose level of 10.1 + 1.16 mmol/l the ICVF level increased to 2.94 + 0.83 %.

These data confirm that hyperglycemia provokes the ICVF level elevation that, in turn, is a poor prognostic sign for coronary heart disease, heart failure and other related diseases.

The present study underscores the relevance of glycaemia control in patients with type 2 diabetes and timely determination of ICVF that will allow to prevent the occurrence of myocardial dyssynchrony and progression of heart failure [11-12].

CONCLUSIONS

1. The hyperglycemia in patients with type 2 diabetes contributes to the development of interstitial collagen volume fraction.

2. The study showed a significant increase of the level of interstitial collagen volume fraction associated with the glycaemia level elevation.

3. A high level of interstitial collagen volume fraction in patients with coronary heart disease and type 2 diabetes can be a predictor of myocardial dyssynchrony development and heart failure progression.

4. A close monitoring of blood glucose levels is required in patients with type 2 diabetes to prevent the complication development.

5. Determination of ICVF should become a routine diagnostic method in all patients with diabetes and subsequent correction of changes is necessary in the early stages of type 2 diabetes.

PROSPECTS FOR FUTURE STUDIES

It is necessary to investigate further the specificfeatures of interstitial collagen changes depending on the therapy application aimed to reduce myocardial fibrosis.

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FEATURES OF SENSITIVITY TO ANTIBACTERIAL DRUGS IN PATIENTS WITH NONSPECIFIC SALPINGOOPHORITIS

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The features of microflora of the vagina in women patients with chronic nonspecific salpingoophoritis were studied, on the basis of which the main etiological factors of the disease, the features of the formation of associations of microorganisms which cause inflammation and the priorities for the adjustment of antimicrobial therapy were set. The investigations made indicate that in patients with chronic salpingoophoritis the changes of microflora of the vagina occur, accompanied by incoordination of its functioning as a single ecosystem, what is manifested by the disorders of microbiological status and widespread antibiotic resistance of the identified pathogens.

KEY WORDS: chronic salpingoophoritis, microflora, microbial associations, antibiotic resistance

ОСОБЛИВОСТІ ЧУТЛИВОСТІ ДО АНТИБАКТЕРІАЛЬНИХ ПРЕПАРАТІВ ПАЦІЄНТОК ХВОРИХ НА НЕСПЕЦИФІЧНИЙ САЛЬПІНГООФОРИТ

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Вивчені особливості мікрофлори піхви у жінок хворих на неспецифічний хронічний сальпінгофорит, на підставі чого виявлені основні етіологічні чинники розвитку захворювання, особливості формування асоціацій мікроорганізмів, які викликають запальний процес та визначені основні напрямки коригування протимікробної терапії. Проведені дослідження свідчать про те, що у пацієнток з хронічним сальпінгоофоритом відбуваються зміни мікрофлори піхви, які супроводжуються дискоординацією її функціонування як єдиної екосистеми, що проявляється порушеннями мікробіологічного статусу та поширеною антибіотикорезистентністю виявлених збудників.

КЛЮЧОВІ СЛОВА: хронічний сальпінгоофорит, мікрофлора, мікробні асоціації, антибіотикорезистентність

ОСОБЕННОСТИ ЧУВСТВИТЕЛЬНОСТИ К АНТИБАКТЕРИАЛЬНЫМ ПРЕПАРАТАМ ПАЦИЕНТОК БОЛЬНЫХ НА НЕСПЕЦИФИЧЕСКИЙ САЛЬПИНГООФОРИТ

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Изучены особенности микрофлоры влагалища у женщин с неспецифическим хроническим сальпингофоритом, на основании чего выявлены основные этиологические факторы развития заболевания, особенности формирования ассоциаций микроорганизмов, которые вызывают воспалительный процесс и определены основные направления коррекции противомикробной терапии. Проведенные исследования свидетельствуют о том, что у пациенток с хроническим сальпингоофоритом происходят изменения микрофлоры влагалища, сопровождающиеся дискоординацией ее функционирования как единой экосистемы, проявляющейся нарушениями микробиологического статуса и обширной антибиотикорезистентностью выявленных возбудителей.

КЛЮЧЕВЫЕ СЛОВА: хронический сальпингоофорит, микрофлора, микробные ассоциации, антибиотикорезистентность

INTRODUCTION

The actuality of preservation and rehabilitation of women's reproductive health

has recently acquired special significance due to the increased number of chronic inflammatory diseases of the pelvic organs in women, lack of information about the pathogenic mechanisms of inflammatory reactions in presence or absence of the microbial factor, with some features of clinical course of chronic salpingoophoritis, what creates considerable difficulties in early diagnostics, with low efficiency of routine methods of treatment. Chronic inflammatory diseases of female pelvic organs are prevalent in the structure of gynecological pathology at the reproductive age with an incidence of 60-65%, and they are the cause of female infertility and menstrual dysfunctions [1, 2]. In modern conditions mixed infections of internal reproductive organs become increasingly important in the etiology of the diseases of the female reproductive system. Perhaps the change of the etiologic factors of infectious inflammatory diseases of the pelvic organs is caused by the adaptability of opportunistic microorganisms to the influence of environmentally unfavorable factors, chemical drugs, etc., by the creation of the conditions for the emergence of the strains resistant to drug influence, which acquired the complex of qualitatively new properties that make them high virulent and resistant to the influence of the immune system [3, 4].

Maintaining the stable qualitative and quantitative composition of the vaginal microbiocenosis is important in providing normal physiological status of the female organism. Normal vaginal bacterial flora is represented by different types of microorganisms, many of which are not yet identified. Quantitative bacteriological analysis of healthy women showed that 1 g of vaginal fluid contains 10^8 cells of aerobic and 10^9 cells of anaerobic bacteria. Leading microorganisms are *Lactobacillus, Peptococcus, Bacteroides, Staphilococcus epidermidis, Corinebacterium spp., Peptostreptococcus spp., Eubacterium*. This list represents the rank location of the dominant microbiota based on concentrations of more than 10^5 CFU per gram [5, 6].

It is reasonable to consider microbial consortium of vaginal mucous membranes as an organized biofilm which specifically changes into pathogenic condition that includes a set of permanent agents such as *Pseudonocardia, Fusobacterium, Haemophylus, Klebsiella, Streptococcus, Staphylococcus epidermidis* and *Clostridium perfringens* and other periodically active community members [7].

Thus, the above-said suggests actuality of further deep study of the pathogenetic features of nonspecific salpingoophoritis on the background of identification of its microbiological features, all the more so since scientific sources suggest the lack of effectiveness of existing methods.

OBJECTIVE

The study aims to improve the treatment of the patients with nonspecific salpingoophoritis on the basis of determination of susceptibility of vaginal microflora to antibiotic drugs.

MATERIALS AND METHODS

The study evaluated the features of vaginal microflora in 70 patients aged 25 to 39 suffering from nonspecific chronic salpingoophoritis compared with the control group (35 healthy women).

The test groups were distributed as follows: group 1 – female patients with a history of chronic salpingoophoritis lasting up to 10 years (n = 35), group 2 – patients with chronic salpingoophoritis lasting more than 10 years (n = 35); group 3 – almost healthy women (comparison group).

For the assessment of the microorganism content in genital secretions of women the tested material was taken from the posterior vaginal vault and subjected to bacteriological examination. The microflora was evaluated by the method of H. Haenel (1979) in the modification of S. K. Kanareykina (1981), under which the following was taken into account: 1) the frequency of occurrence of the microorganisms in this biotope; 2) general dissemination; 3) the quantity and type composition of: a) lactobacilli; b) streptococci; c) staphylococci; d) enterobacteria; e) fungi of the genus Candida; 4) microbial associations [6]. Removal of isolates from vaginal secretions and cervical scrape was made by the conventional methods in microbiology. Enzymatic identification was made with the help of identification sets MICRO-LA-TEST®, designed for providing standard identification using micro methods. They allow identification of most clinically important microorganisms in short terms.

The sensitivity of the isolates to antimicrobial agents with different mechanisms of action on a microbial cell was studied by

means of microtest system «TNK test» with semiquantitative registration of results.

The data were processed after building the databases in Microsoft Excel, Statistica 7.0. For statistical evaluation of the results parametric criteria were used (mean – M, standard deviation sd) and non-parametric criteria (absolute (n, number) and relative (percentage (p, %) and the average error of rate (sP), criterion $\chi 2$) units). Statistical reliability of differences between groups was evaluated by nonparametric U-Mann-Whitney test. The results were considered adequate at the significance level $p < 0,05$ and $p < 0,01$.

RESULTS AND DISCUSSION

As a result of the study of the female patients of groups 1 and 2 violations of the vaginal microbiocenosis were found. Analyzing the obtained data, we can prove that the most frequent microorganisms removed from the vaginal discharge were: *Peptostreptococcus spp* – 78 % and 75 %, *Enterococcus* – 69 % and 57 %, *S.aureus* – 62,9 % and 60,1 %, *E.coli* – 64,2 % and 69,3 %, *Fusobacterium spp* – 61,0 % and 58.0 %; *S. pyogenes* – 58,0 % and 60 %, *Candida spp* – 47,0 % and 44 %.

During bacteriological study from biomaterial the isolates were typically removed in associations (Fig.).

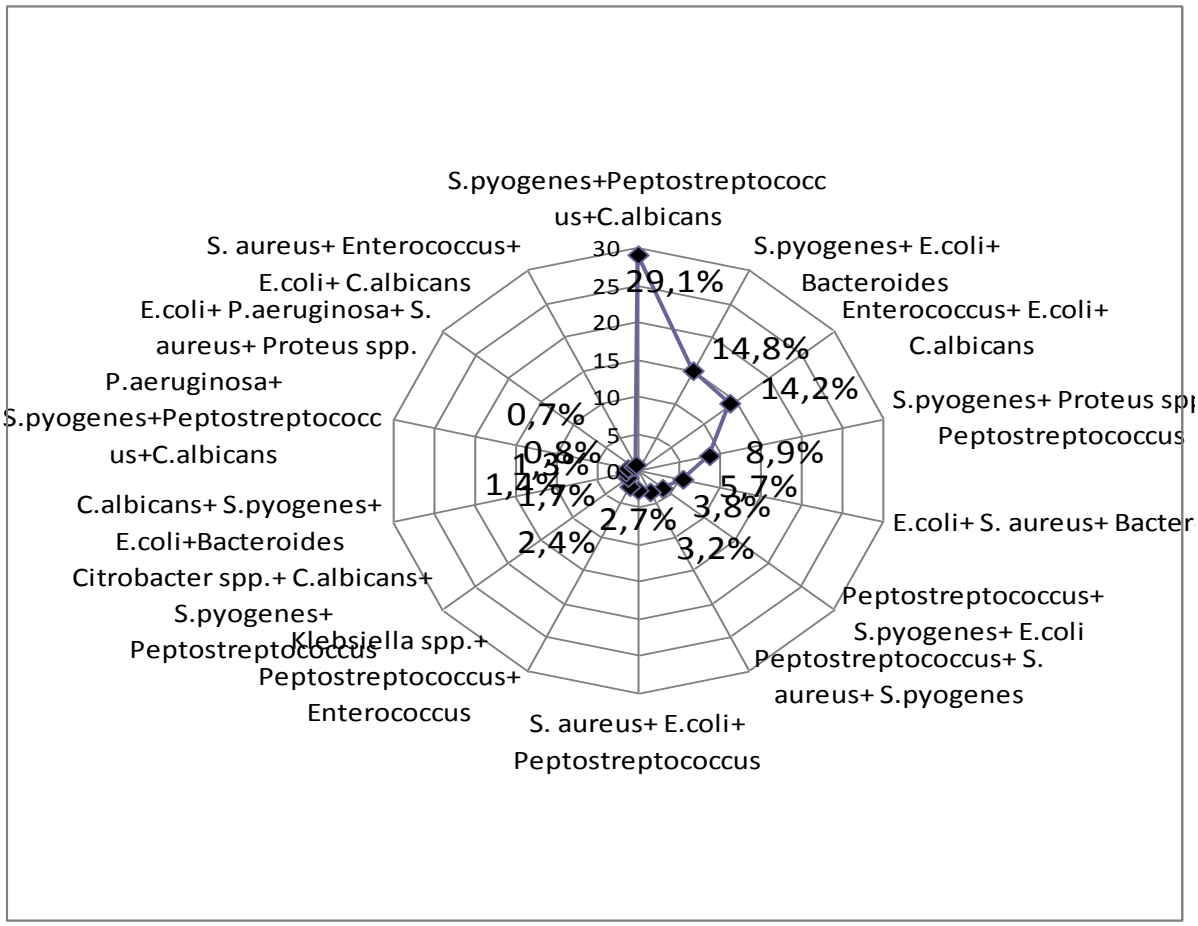

Fig. Associations of isolates separated in salpingoophoritis

Among the coccal flora there were staphylococci, which were found in the patients of two test groups. Dissemination with staphylococci was averaged $1,7 \cdot 10^5 \pm 1,2 \cdot 10^4$ and $4,1 \cdot 10^4 \pm 1,5 \cdot 10^3$ CFU per unit substrate respectively, the most frequent was *S.aureus* with the density of microbial colonization $6,3 \cdot 10^4 \pm 1,2 \cdot 10^3$ and $7,5 \cdot 10^4 \pm 1,3 \cdot 10^3$ CFU per unit substrate respectively. Microbiocenosis of anaerobic flora in patients was diverse. Thus, in the vaginal microflora of the test groups *Veillonella spp* and *Prevotella spp.* were found with the dissemination equal to $1,8 \cdot 10^4 \pm 1,2 \cdot 10^4$ and $2,9 \cdot 10^4 \pm 1,6 \cdot 10^3$, and

$1{,}5 \cdot 10^4 \pm 1{,}6 \cdot 10^4$ and $3{,}7 \cdot 10^3 \pm 1{,}4 \cdot 10^2$ CFU per unit substrate. *Bacteroides spp* was detected with dissemination of $4{,}4 \cdot 10^2 \pm 1{,}8 \cdot 10^1$ and $1{,}3 \cdot 10^3 \pm 1{,}6 \cdot 10^2$ CFU per unit substrate. At the same time in the microbiocenosis of vagina *Propionibacterium spp.* was registered. Its colonization density was equal to $1{,}9 \cdot 10^5 \pm 1{,}6 \cdot 10^4$ and $5{,}7 \cdot 10^4 \pm 1{,}2 \cdot 10^3$ CFU per unit substrate in accordance.

The results of the comparative evaluation of the sensitivity to antimicrobial drugs of therapeutic purpose of the isolates which were more frequently disseminated in patients with salpingoophoritis (staphylococci, streptococci, enterobacteria and obligate anaerobes) showed that the incidence of identification of the isolates of Staphylococcus resistant to antimicrobial drugs was much different and depended on the duration of an inflammatory process (tab. 1).

Table 1

Antibiotic resistance of Staphylococcus isolates

Antibiotics	Rate of resistant strains (M ± м)		
	Group 1	Group 2	Group 3
Cefepime	5,6 ± 5,4	4,4 ± 16,6*#	2,0 ± 3,3
Ceftazidime	11,1 ± 7,4	7,0 ± 6,2* *	3,0 ± 3,3
Ciprofloxacin	12,0 ± 3,6	11,1 ± 2,5**	7,0 ± 3,3
Rifampicin	76,0 ± 3,6	44,4 ± 16,6* *	31,0 ± 3,3
Erythromycin	88,9 ± 7,5	91,2 ± 6,2*	59,0 ± 1,2
Vancomycin	15,0 ± 3,6	13,0 ± 6,2**	9,0 ± 3,3
Lincomycin	77,7 ± 2,8	94,4 ± 6,6*	50,0 ± 5,2
Gentamicin	91,1 ± 5,5	91,3 ± 6,2*	69,0 ± 3,3*
Amikacin	10,0 ± 3,6	11,1 ± 2,5*	2,0 ± 3,3
Kanamycin	93,3 ± 4,1	93,0 ± 6,2*	57,0 ± 4,9
Ampicillin	61,1 ± 4,5	92,8 ± 6,2* *	50,0 ± 5,2
Oxacillin	95,6 ± 5,4	96,3 ± 2,2*	70,0 ± 3,3
Penicillin	72,2 ± 10,6	97,2 ± 1,2* *	50,0 ± 1,2
Amoxicillin	90,0 ± 3,6	93,1 ± 2,2*	40,0 ± 3,3
Chlorhexidine	6,0 ± 1,6	4,9 ± 0,6* ◙	1,0 ± 0,3

Note: *$p<0{,}001$; **$p<0{,}01$; # $p<0{,}05$ compared with the control group (group 3);
* $p<0{,}001$; ◙ $p<0{,}05$ compared with the patient group 1.

Staphylococcus isolates were characterized by variable sensitivity to the studied drugs. The most resistant to antimicrobial drugs Staphylococcus strains were taken from the patients of groups 1 and 2. Regarding penicillin the percentage of resistant strains in the patients of group 2 was 97.2 %; the percentage of majority of cephalosporins – from 2.0 % to 11.1 %. Generally, most Staphylococcus isolates were poly-resistant.

As shown in Table 2, among Enterobacteria extracted from the patients of test groups, the rate of resistant strains was high in all groups of study. Before cephalosporins resistant strains percentage was higher for Enterobacterium isolates from the patients of group 1 – 9.3 to 16.7 %.

Table 2

Antibiotic resistance of Enterobacterium isolates

Antibiotics	Rate of resistant strains (x ± Sx)		
	Group 1	Group 2	Group 3
Cefepime	11,3 ± 0,8	16,7 ± 1,0**	2,0 ± 0,3
Ceftazidime	9,3 ± 0,8	6,7 ± 1,0*◙	3,0 ± 0,3
Ciprofloxacin	81,3 ± 8,8	86,7 ± 7,0*	7,0 ± 0,3
Rifampicin	56,3 ± 2,4	96,2 ± 1,8**	31,0 ± 3,3
Gentamicin	93,8 ± 6,1	97,8 ± 6,2*	69,0 ± 3,3
Amikacin	93,8 ± 6,1	93,0 ± 1,8*	2,0 ± 0,3
Kanamycin	81,3 ± 8,8	88,9 ± 4,7*	57,0 ± 4,9
Ampicillin	81,3 ± 8,8	96,0 ± 1,8*◙	50,0 ± 5,2
Amoxicillin	97,0 ± 2,0	98,0 ± 1,8#	83,3 ± 6,8
Carbenicillin	75,0 ± 6,8	88,9 ± 4,7	73,3 ± 6,8
Levomycetin	98,0 ± 1,0	98,2 ± 1,8*	24,0 ± 2,5
Chlorhexidine	5,0 ± 3,6	4,4 ± 0,6	1,0 ± 0,3

Note: *p < 0,001; # p < 0,05 compared with the control group;
* P < 0.001; ◙ p < 0.05 compared with group 1

The data in Table 3 indicate that in patient groups 1 and 2 of the number of resistant strains of streptococci ranged from 11.0 % to 98.6%.

Table 3

Antibiotic resistance of Streptococcal isolates

Antibiotics	Rate of resistant strains (x ± Sx)		
	Group 1	Group 2	Group 3
Clindamycin	69,0 ± 2,5	28,6 ± 2,1**	1,0 ± 0,15
Erythromycin	73,3 ± 7,6	88,6 ± 2,1**	10,0 ± 0,9
Ceftriaxone	15,0 ± 1,1	17,7 ± 1,4*	9,0 ± 0,2
Cefotaxime	16,7 ± 1,8	15,7 ± 1,4*	8,0 ± 0,9
Ampicillin	93,3 ± 2,6	98,6 ± 1,1*	50,0 ± 5,0
Azithromycin	90,0 ± 2,1	88,6 ± 2,1*	5,0, ± 2,8
Vancomycin	11,0 ± 1,5	11,0 ± 1,1*	1,0 ± 0,1
Levomycetin	86,7 ± 6,8	92,85 ± 3,2*	24,0 ± 2,5
Ofloxacin	28,9 ± 2,5	28,6 ± 2,1*	1,0 ± 0,15
Sisomicin	12,0 ± 1,5	14,3 ± 1,4	15,0 ± 1,6
Chlorhexidine	13,0 ± 3,6	14,4 ± 4,6*◙	1,0 ± 0,3

Note: * p < 0.001; ** p < 0.01; # P < 0.05 compared with the control group;
* P < 0,001; • p < 0,01; ◙ p < 0.05 compared with group 1.

Evaluation of the resistance of the isolates to antimicrobial agents using microplate «TPK G -» and «TPK G + » (tab. 4) showed that all strains were variable to antimicrobial drugs and

most strains were resistant to ampicillin and doxycycline and moderately resistant to gentamicin. The analysis of the data obtained allowed to find out that all isolates had multiple antibiotic resistance. The studies showed that the isolates were resistant to ampicillin, gentamicin and doxycycline – the growth of culture was observed in the microplate cells with higher and lower concentrations of antimicrobial preparations.

Table 4

The sensitivity of isolates to antimicrobial drugs inoculated in microplate cells «TPK G -» and «TPK G + »

Antimicrobial drugs inoculated in microplate cells «TPK G -» and «TPK G + »	Staphylococci			Streptococci			Enterobacteria		
	R %	I %	S %	R %	I %	S %	R %	I %	S %
Cefotaxime	4	4	92	4	7	89	80	9	11
Ciprofloxacin	11	1	88	30	4	66	86	2	12
Gentamicin	94	6	0	97	3	0	97	3	0
Ampicillin	69	31	0	93	6	1	98	2	0
Doxycycline	96	4	0	94	6	0	88	12	0

Thus, in determining the susceptibility of isolates to antibiotics it has been discovered that most of them were multiresistant (89.2 %). Variable sensitivity to antimicrobial agents related to glycopeptides, fucidins, rifampicin and lincozamides was observed.

Thus, the development of the diseases of microbial etiology depends on the persistent properties of microorganisms aimed for the inactivation of the factors of natural resistance of the organism. The type composition and biological properties of the vaginal microflora in women with nonspecific salpingoophoritis were studied and it was shown that inflammatory diseases of internal reproductive organs occur on the background of dysbiotic disorders characterized by the release of microorganisms with high persistent properties. The latter obviously play an important role in the pathogenesis of inflammatory diseases and dysbiotic conditions of internal reproductive organs.

Based on the above it was confirmed that the occurrence and intensity of inflammatory process depend on the individual fluctuations in qualitative and quantitative composition of microflora of the vagina.

The main practical problem of the diagnosis verification primarily concerns timely determination of the cause of inflammatory process and is associated with the demand of accurate typing of the etiological factor of salpingoophoritis. During the detection of microbial associations the difficulties which arise during the treatment of patients with salpingoophoritis have become clear. The first reason of any failure is persistent diagnostics of the etiological factors while ignoring the pathogenic potential of normal microflora. The second reason is common difficulties in transporting the drugs to the focus of inflammation. The third cause little known to clinicians is group resistance of antibiotics and other effects (quorum sensing) of locus microbiota organized in biofilm.

From the overview of the information on the distribution of microbial associations during the inflammation of the pelvic organs, their multiple antibiotic resistance, antibiotic drugs should be administered immediately after clarifying the nosological diagnosis and before getting the results of bacteriological research. After receiving the results of the bacteriological study the mode of antimicrobial therapy should be adjusted for the selected microflora and its antibiotic sensitivity. Therefore, adequate microbiological diagnosis of ascending infection which causes development of nonspecific salpingoophoritis should be given enough attention as well as to the choice of a mode of therapy.

PROSPECTS FOR FUTURE STUDIES

The current stage of the development of medicine is characterized by insufficient effectiveness of therapy of ascending infection

that leads to salpingoophoritis and then to its chronic course. To a certain extent this is explained by to the presence of mechanisms of protection of pathogens from damaging factors. One of such mechanisms is the ability to form biofilm. Therefore, the study of the ability to form biofilms by microorganisms will allow a new approach to the administration of antimicrobial therapy, creation of the conditions for further investigations on the realization of rational therapeutic measures.

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CLINICAL PRESENTATIONS OF ARTERIAL HYPERTENSION DEPENDING ON THE QTc INTERVAL DURATION OF ECG

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The relationship between the duration of the complex QTc ECG and clinical signs of arterial hypertension (AH) in 54 patients (16 men and 38 women) 1-3 degree and I-III stage, mean age 58 ± 18 years, was investigated. 3 classes of QT interval duration were allocated: classified shortened (< 320 ms), normal (> 320 ms and < 440 ms), classified prolonged (> 440 ms). The binomial distribution of frequencies of studied parameters in classes of the QTc interval for alternative criteria was determined. The duration of the QTc interval in the sampling was 350 ms – 490 ms. The proportion of the normal range (> 320 ms and < 440 ms) was 0.85, classified prolonged (> 440 ms) – 0.15. The probability of occurrence of QTc prolongation ECG increased in elderly patients, obesity, abusing of alcohol, mild and moderate degree and stage II AH, diabetes mellitus, atherosclerotic cardiosclerosis, stable angina functional class (FC) II, HF FC III and II A stage. Dependencies of the elongated QTc of ECG from the sex of the patients have not been established.

KEY WORDS: arterial hypertension, duration of the QTc interval of ECG

КЛІНІЧНІ ПРОЯВИ АРТЕРІАЛЬНОЇ ГІПЕРТЕНЗІЇ ЗА РІЗНИХ ДІАПАЗОНІВ ТРИВАЛОСТІ ІНТЕРВАЛУ QTc ЕКГ

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Досліджено зв’язок між тривалістю комплексу QTc ЕКГ та клінічними ознаками АГ у 54 пацієнтів з АГ (16 чоловіків та 38 жінок) 1-3 ступені та I-III стадії, середнім віком 58 ± 18 років. Виділено 3 класи тривалості інтервалу QTc: класифікований укорочений (< 320мс с), нормальний (> 320 та < 440мс), класифікований подовжений (> 440 мс). Визначалась біноміальна розповсюдженість частот поширенності вивчених показників в класах інтервалу QTc для альтернативних критеріїв. Тривалість інтервалу QTc в вибірці склала 350мс – 490мс. Питома вага нормального інтервалу (> 320 та < 440мс) дорівнювалася 0,85, класифікованого подовженого (> 440мс) – 0,15. Ймовірність поширенності подовженого інтервалу QTc ЕКГ збільшувалася серед пацієнтів похилого віку, з ожирінням, які зловживали алкоголем, мали м’який та помірний ступені, а також II стадію АГ, наявний цукровий діабет, атеросклеротичний кардіосклероз, стабільну стенокардію II ФК, СН III ФК та IIA стадії. Залежності подовженого інтервалу QTc ЕКГ від статі у пацієнтів з АГ не встановлено.

КЛЮЧОВІ СЛОВА: артеріальна гіпертензія, тривалість інтервалу QTc ЕКГ

КЛИНИЧЕСКИЕ ПРОЯВЛЕНИЯ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ ПРИ РАЗЛИЧНЫХ ДИАПАЗОНАХ ДЛИТЕЛЬНОСТИ ИНТЕРВАЛА QTc ЭКГ

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Исследована связь между продолжительностью комплекса QTc ЭКГ и клиническими признаками АГ у 54 пациентов с АГ (16 мужчин и 38 женщин) 1-3 степени и I-III стадии, средний возраст 58 ± 18 лет. Выделено 3 класса продолжительности интервала QTc: классифицированный укороченный (<320мс), нормальный (> 320 и < 440мс), классифицированный удлиненный (> 440 мс). Определялось биномиальное распространение частот встречаемости изученных показателей в классах интервала QTc для альтернативных критериев. Продолжительность интервала QTc в выборке составила 350мс – 490мс. Удельный вес нормального интервала (> 320 и < 440мс) составлял 0,85, классифицированного удлиненного (> 440мс) – 0,15. Вероятность встречаемости удлиненного интервала QTc ЭКГ увеличивалась среди пациентов пожилого возраста, с ожирением, которые злоупотребляли алкоголем, имели мягкую и умеренную степени, а также II стадию АГ, сахарный диабет, атеросклеротический

кардиосклероз, стабильную стенокардию II ФК, СН III ФК и IIА стадии. Зависимости удлиненного интервала QTc ЭКГ от пола у пациентов с АГ не установлены.

КЛЮЧЕВЫЕ СЛОВА: артериальная гипертензия, длительность интервала QTc ЭКГ

INTRODUCTION

Arterial hypertension (AH) is one of the most common chronic diseases, which significantly increases the risk of cardiovascular complications and premature death. Prevalence of AH in different countries varies between 15-30 %. According to official statistics in Ukraine in 2009 was registered more than 12 million of patients with AH, it is about 1/3 of the adult population. With time, including due to the aging of population in developed countries, the prevalence of hypertension will increase [1-2].

Prolongation or reduction of the QT interval duration outside the defined range is regarded as a risk factor of critical arrhythmias [3-5]. Electrophysiological phenomenon of prolonged interval QT is the independent predictor of fatal arrhythmias that lead to sudden cardiac death [6-8].

At present there is no information in the literature about the relationship between the duration of QTc and clinical signs of AH.

The research was conducted as part of research work «Development and research of system of automatic control of heart rate variability», state registration 0109U000622.

OBJECTIVE

The purpose of the work was to study the relationship between QTc duration on ECG and clinical signs of AH for the development of improvement proposals to its diagnosis and treatment.

MATERIALS AND METHODS

In the Kharkiv outpatient clinic № 24 54 patients (16 men and 38 women) aged from 45 to 87 years with duration of AH 58 ± 18 years were examined. From 54 patients in 25 was mild degree, 20 - moderate and 9 - severe. Stage I AH occurred in 15, stage II - in 33, stage III - in 6 patients. Ischemic heart disease (IHD) was diagnosed in 43 patients, specifically: stable exertional angina with functional class (FC) I occurred in 6, II FC - in 3, postinfarction cardiosclerosis (PC) - in 2, atherosclerotic cardiosclerosis (AC) - in 32. In 40 patients was presented symptoms of heart failure (HF), specifically: FC I - in 14, FC II - in 23, FC III - in 3. HF stage I occurred in 34 persons, stage IIA - in 6 persons. The study did not include patients with stable exertional angina FC III, acute cardiovascular diseases, HF II B - III stage and FC IV.

For measurement of the QTc interval duration was performed ECG on the computer electrocardiographs «Cardiolab +». QTc interval duration was measured in leads II, V1, V5, V6 (three consecutive complexes) with maximum choice for intervals and leads. SBP and DBP were measured by tonometer Korotkov's «Microlife BP AG1-20».

3 classes of QT interval duration were allocated: classified shortened (< 320 ms), normal (> 320 ms and < 440 ms), classified prolonged (> 440 ms). Probabilities of occurrence of sex, age, weight of patients, duration of AH, the presence of bad habits, degree and stage of AH, FC of stable angina, FC and stage of HF in selected classes of QTc interval duration were calculated [9-11].

With Microsoft Excel 2010 was determined the binomial distribution of frequencies of studied parameters (P - probability and standard deviation σ, as an absolute measure of its variations, %) in classes of QTc interval for alternative criteria. Reliability of differences in parameters between groups of patients was determined using t - Student's test. Statistically reliable data was taken with significance level $p < 0.05$.

RESULTS AND DISCUSSION

The duration of the QTc interval in the sampling was 350 ms - 490 ms. The proportion of the normal range (> 320 ms and < 440 ms) was 0.85, classified prolonged (> 440 ms) - 0.15. Classified shortened QT interval of ECG (< 320 ms) were not detected, due to its low prevalence [3-5].

The frequency of occurrence of different QTc interval duration classes in patients with AH depending on clinical signs presented in the table.

Table

The frequency of occurrence of different QTc interval duration classes in patients with AH depending on clinical signs

Parameters			Total sampling		Classes of QTc interval duration, ms		
			P	σ	≥ 320< 440 (P)	≥ 440 (P)	σ
Total patients		54	100	0,00	0,85	0,15	0,36*
Age (years)		Mature	0,67	0,47*	0,86	0,14	0.35*
		Elderly	0,30	0,46*	0,81	0.19	0,39*
		Senile	0,03	0,17*	1	0	0,00
Sex		Males	0,30	0,46*	0,88	0,12	0,33*
		Females	0,70	0,46*	0,84	0,16	0,37*
Weight (BMI, kg/m²)		Normal	0,09	0,29*	1	0	0,00
		Overweight	0,37	0,48*	0,90	0,10	0,30*
		Obesity	0,54	0,5*	0,79	0,21	0,41*
Bad habits		Smoking	0,20	0,4*	0,82	0,18	0,39*
		Alcohol	0,06	0,24*	0,67	0,33	0,47*
Duration of AH (years)		0-5	0,54	0,5*	0,79	0,21	0,41*
		5-10	0,22	0,41*	0,92	0,08	0,27*
		>10	0,24	0,43*	0,92	0,08	0,27*
AH	Degree	Mild	0,46	0,5*	0,84	0,16	0,37*
		Moderate	0,37	0,48*	0,85	0,15	0.37*
		Severe	0,17	0,38*	0,89	0,11	0,31*
	Stage	I	0,28	0,45*	1,00	0,00	0,00
		II	0,61	0,49*	0,79	0.21	0.41*
		III	0,11	0,31*	0,83	0.17	0.38*
ICH	Total		0,80	0,4*	0,86	0,14	0.35*
	Stable angina, FC	I	0,11	0,31*	1,00	0,00	0,00
		II	0,06	0,24*	0,67	0.33	0,47*
	Cardiosclerosis	PC	0,04	0,20*	1,00	0,00	0,00
		AC	0,59	0,49*	0,84	0,16	0,37*
HF	FC	I	0,26	0,44*	0,93	0,07	0,25*
		II	0,43	0,50*	0,83	0,17	0,38*
		III	0,06	0,24*	0,67	0,33	0,47*
	Stage	I	0,63	0,48*	0,85	0,15	0,37*
		IIA	0,11	0,31*	0,83	0,17	0,38*

* - $p < 0,05$

Obtained data was statistically significant and was within the significance of $p < 0.05$.

In the studied patient population mature age formed the largest portion, less than half - the elderly and the least - senile age. The occurrence of normal QTc interval was greatest among patients of mature age, and prolonged - among elderly.

Female patients in the sampling were substantially prevailed. The occurrence of normal QTc interval among males was slightly higher in compare with the females and prolonged - conversely.

Greater proportion of patients with AH was formed by persons with obesity and overweight. The occurrence of normal QTc interval was greatest among patients with overweight and prolonged - among patients with obesity [12].

As for the bad habits, greater proportion of long QTc ECG was registered among persons who abused alcohol.

Greater proportion of patients was with duration of AH from 0 to 5 years and equally less - from 5 to 10 years and from 10 years. The occurrence of normal QTc interval was greatest with disease duration from 5 to 10 years and from 10 years, and prolonged QTc - with disease duration from 0 to 5 years. Most likely this is due to the predominance of the given category of patients in study and progression of AH.

Most of the study sampling consisted of patients with mild to moderate AH. The occurrence of normal QTc interval was greater among individuals with mild and moderate and stage II AH. Most likely this is due to the irregular, before inclusion to the study, taking of medications.

The largest share of patients with ischemic heart disease was persons with atherosclerotic cardiosclerosis and stable angina FC I. The occurrence of normal QTc interval was greater among individuals with atherosclerotic cardiosclerosis.

Greater proportions of patients with heart failure were persons with I-II FC and stage I HF. The occurrence of normal QTc interval was largest among individuals with HF FC II-III and IIA stage [13-14].

CONCLUSIONS

1. In the study population of patients with AH QTc interval duration of ECG was ranged from 350 ms to 490 ms. The proportion of the normal range (> 320 ms and <440 ms) was 0.85, classified prolonged (> 440 ms) - 0.15. Classified shortened QT interval of ECG (< 320 ms) were not detected.

2. The probability of occurrence of QTc prolongation of ECG in patients with AH increased amount elderly patients, with obesity, abusing of alcohol, mild and moderate degree and stage II AH, diabetes mellitus, atherosclerotic cardiosclerosis, stable angina functional class (FC) II, HF FC III and II A stage.

3. Dependencies of the elongated QTc of ECG from the sex of the patients have not been established.

PROSPECTS FOR FUTURE STUDIES

It is appropriate to find relationships between the duration of the QTc interval of ECG, clinical course and consequences in patients with AH for improving of its diagnosis and treatment.

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Clinical case

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POLYMORBIDITY DOES NOT DETERMINE POLYPHARMACY

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Combination of polymorbidity and polypharmacy is reviewed on the example of clinical case. Clinical examination, the clinical diagnosis, recommendations for lifestyle modification choice of optimal therapy are outlined in patient with polymorbid disease.

KEY WORDS: polymorbidity, polypharmacy, rational pharmacotherapy, quality of life, disease prevention

ПОЛІМОРБІДНІСТЬ НЕ ВИЗНАЧАЄ ПОЛІПРАГМАЗІЮ

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На прикладі клінічного випадку розглядається поєднання проблеми поліморбідності та поліпрагмазій. Описані діагностика, постановка заключного клінічного діагнозу та рекомендації по модифікації способу життя та вибору оптимальної терапії у пацієнта з поліморбідною патологією.

КЛЮЧОВІ СЛОВА: поліморбідність, поліпрагмазія, раціональна фармакотерапія, якість життя**,** профілактика

ПОЛИМОРБИДНОСТЬ НЕ ПРЕДОПРЕДЕЛЯЕТ ПОЛИПРАГМАЗИЮ

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На примере клинического случая рассматривается сочетание проблемы полиморбидности и полипрагмазии. Описаны диагностика, постановка заключительного клинического диагноза и рекомендации по модификации образа жизни и выбора оптимальной терапии у пациента с полиморбидной патологией.

КЛЮЧЕВЫЕ СЛОВА: полиморбидность, полипрагмазия, рациональная фармакотерапія, качество жизни, профилактика

INTRODUCTION

Recent studies discuss the problem of medical care for patients with concomitant comorbidity and associated polypharmacy [1-3]. Accumulation of chronic diseases comes along with aging [4]. An interaction of diseases, involution processes in the body and effects of drug therapy significantly alter clinical picture, course of the disease, nature and severity of the complications; as well as worsens patient's quality of life [1].

Such terms as polymorbidity (polymorbid disease or polymorbid condition) and polypharmacy are often used in English scientific literature. Polymorbidity is defined as the existence of several chronic health disorders in one individual. Whereas, polypharmacy is a simultaneous appointment of drugs or medical procedures to patient, which often appears to be unjustified and irrational.

Polypharmacy in consequence with polymorbidity leads to a sharp rise in the

occurrence of systemic, adverse effects of medicines. Such unwanted side effects lead to new clinical symptoms. Unfortunately, doctors do not always take those symptoms into consideration, as they are often seen as symptoms of polymorbidity and not as effects of polypharmacy. Therefore, this leads to prescription of higher amount of medications [1, 5].

The importance of the problem of combination of polymorbidity and polypharmacy is shown in the given clinical case.

CLINICAL CASE

Man, 49 years old, economist, resident of urban area.

COMPLAINTS

For the past month patient complained of pain behind the breastbone without irradiation, occurring both during fast walk for up to 100 m and at rest; pain disappears within 10 minutes; shortness of breath of mixed character; periodic heartbeat, appearing without a clear connection with the provoking factors and disappears by itself ; recurrent headache of a compressive character in the temporal region that appears as a result of elevated blood pressure (BP) over 150/90 mm Hg; periodic dry cough in the morning; heartburn after heavy, spicy and fried meals; aching pain in the epigastrium, going away after an intake of liquid or warm food; numbness of 3-4 fingers mostly at night.

ANAMNESIS MORBI

Rise in blood pressure (BP) with maximum numbers 170/90 mm Hg from his youth (diagnosis: vegetative-vascular dystonia (VVD) of hypertensive type). Usual blood pressure - 140/90 mm Hg. He was treated in the outpatient department with antihyper-tensive drugs taken irregularly.

2012: Headache. Self-medication with analgesics (spasmalgon).

2014: Numbness of 3- 4 fingers. Patient did not seek for medical care.

8 Oct 2015: Patient felt pain behind the breastbone for the first time.

20 Oct 2015: Patient was admitted to hospital by administrative district with a preliminary diagnosis: Coronary artery disease (CAD): unstable angina (de - novo). Arterial hypertension (AH) stage II, 2 degree. Heart failure (HF) 0-1 stage. Very high risk.

Drug therapy: Nebivolol 5 mg, Atorvastatin 20 mg, Trimetazidine 35 mg, Bellalginum. Therapy was ineffective.

28 Oct 2015: Patient was sent to STPI «Central clinical hospital Ukrzaliznici» for the examination and selection of therapy in the cardiology department.

ANAMNESIS VITAE

Patient lives alone in an isolated apartment. He eats irregularly, does not follow a diet.

He had frequent pneumonia in childhood. Patient experiences acute respiratory infections (3-4 times a year).

Since 1995 - chronic bronchitis with exacerbations in spring and autumn period. In the period of exacerbation - the sputum was whitish. Self-medication.

2002 - Burn (head, hands, neck, torso) disease.

Since 2008 - decrease in visual acuity.

2014- health resort treatment in Mirgorod with a diagnosis of chronic gastritis. On gastroscopy - gastritis, acute duodenitis, deformation of duodenal bulb, gastro-esophageal reflux. Patient was released from the health resort treatment with improvements, medication therapy was effective.

Patient denies viral hepatitis, tuberculosis, sexually transmitted diseases. Allergic anamnesis is not burdened. He smoked from 1983 to October 2015 - 1 pack a day (32 pack/years). No abuse of alcohol.

Hereditary history burdened by coronary heart disease and hypertension.

OBJECTIVE EXAMINATION

Patient's condition is satisfactory. He is active. Height - 178 cm, weight - 119 kg, body mass index (BMI) = 37,5 kg/m^2. Skin has scarring after burn disease (head, neck, arms, torso). Patient has hernial protrusion of the white line of the abdomen without evidence of infringement. Peripheral lymph nodes: submandibular, axillary and inguinal lymph nodes soft consistency, painless, moderately agile and not soldered to each other and the skin. Lobes of the thyroid gland are not palpable, the isthmus is palpated in the form of a uniform cross-strand smooth, 1 cm wide. Musculoskeletal system - marked tenderness at paravertebral points in the cervical-thoracic spine. There is a mild lung sound above lungs, vesicular breathing and single dry rales on the exhale in the lower parts in auscultation.

Activity of the heart is rhythmic, heart rate (HR) 60 beats/min. Heart sounds are muffled. BP is 130/80 mm/Hg on hypotensive therapy. Abdomen is enlarged. A moderate pain in the epigastric region on deep palpation is present. Liver sticks out below the rib cage for about 1.5-2 cm, painless. The spleen palpated 1 cm below the left costal arch. Pasternatsky's symptom is negative on both sides. Physiological functions: normal. No swelling.

LABORATORY AND INSTRUMENTAL TESTS

Complete blood count (CBC): relative lymphocytosis (39.1 %), thrombocytosis (428 K/UL).

Urinalysis: figures are in the normal ranges.

Biochemical analysis of blood: figures are in the normal ranges.

Cardiac markers: Troponin I < 0.01μg/l, CK-MB – in the normal range.

Analysis of lipid: atherogenic index is increased (3.56 mmol/l); high blood triglyceride level (2.48 mmol/l)

ECG showed sinus rhythm, regular. Heart rate 51 beats/min. Violation of intraatrial conduction. Nonspecific intraventricular conduction disturbances. The syndrome of premature repolarization of the ventricles. Violation of repolarization processes on the postero-lateral wall of the left ventricle in the form of flattened or negative T wave.

Echocardiography: The heart cavity is not expanded, thickened myocardium, and zones of akinesia and hypokinesia was not found, valves are intact. EF – 75 %.

Coronary angiography (CA): right type of coronary blood supply. Diffuse atherosclerotic lesions and calcification of coronary arteries. 20 % occlusion of the left coronary artery and 40 % occlusion of the right coronary artery, 100 % occlusion of the circumflex artery.

Ultrasound of abdominal and retro-abdominal organs: diffuse changes of liver and pancreas parenchyma without magnification. Hepatosplenomegaly. Microcalculosis of kidneys.

Gastroscopy 2.11.15: gastroesophageal reflux, gastritis, deformation of the duodenal bulb, erosive duodenitis.

Gastroscopy 12.11.15 (after therapy): gastroesophageal reflux, deformation of the duodenal bulb.

Consultation of ophthalmologist: Angio-pathy of the retina of 2 degrees.

Consultation of the surgeon: hernial protrusion of the white line of the abdomen without evidence of infringement.

Recommend tests: repeat CBC, daily monitoring of blood pressure, ECG dynamics, spirometry, x-ray chest, x-rays of the cervical-thoracic spine, gastroscopy with biopsy, esophageal pH monitoring, consult a pulmonologist, neurologist.

DIAGNOSIS

The underlying disease: Coronary heart disease: Acute coronary syndrome. Unstable angina (de-novo). Coronary angiography (16.11.15): Diffuse atherosclerotic lesions and calcification of coronary arteries. 20 % occlusion of the left coronary artery and 40 % occlusion of the right coronary artery, 100 % occlusion of the circumflex artery. Arterial hypertension stage III, 2 degree. Very high additional risk. 1-st stage of heart failure, 2nd functional class with preserved systolic function (EF=75 %).

Comorbid conditions: COPD. COB stage I-II? LF stage 0. Erosive duodenitis, deformation of the duodenal bulb. Chronic superficial gastritis. Gastro-esophageal reflux disease without esophagitis. Obesity 2 degree. Midline hernia without obstruction. Chronic kidney disease stage 0. Microurolitiasis. Osteochond-rosis of the cervical-thoracic spine?

TREATMENT RECEIVED IN HOSPITAL

Nebivolol 2.5 mg in the morning, Clopidogrel 75mg , Enoxaparin 80mg 2 p/day, Atorvastatin 40 mg in the evening, Isosorbide dinitrate 10 mg 2 p/day, Pantoprazole 40 mg 2 p/day – 10 days, Famotidinum 40 mg in the evening - 10 days, De-Nol 240мг 2 p/day - 10 days, Almagel 1 tbsp 3 p/day - 10 days.

RECOMMENDATIONS

1. Lifestyle modification: lipid-lowering diet with restriction of refined carbohydrates, increase of the intake of vegetables and fruits (the patient has gastritis and gastro-esophageal reflux disease - stewed and baked), restriction of consumption of table salt, regular exercise, walks in the fresh air, physiotherapy aimed at reducing manifestations of osteochondrosis.

2. Drug therapy: Nebivolol is 1.25 mg in the morning (under the control of heart rate and blood pressure), Clopidogrel – 75 mg 1 time a day continuously, Rosuvastatin 10 mg 1 time

per day for a long time, Nitroglycerin (tablet or spray) as needed.

3. Surgical treatment: stenting of the circumflex artery.

On the background of optimally chosen therapy the patient's condition has stabilized, marked improvement of hemodynamic parameters.

CONCLUSIONS

When treating patients with polymorbid pathology, in order to avoid polypharmacy, it is suggested to prescribe a minimum quantity of pharmacological agents, avoiding mutually exclusive drugs; to apply only rational polytherapy and fixed combinations of drugs.

In the given clinical case polymorbidity is present, but it doesn't mean that there is a need for doctor to prescribe high variety of medications. We consider that it is important to focus first on a treatment of the primary cardiovascular disease, while related disease entities should be treated medically and through physiotherapy interventions (physiotherapy, massage, dietary recommendations) only if necessary. Furthermore, it is important to constantly take preventive measures aimed at avoiding progression and complications of those diseases.

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Review

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THE EFFECTS OF STATIN THERAPY ON PNEUMONIA OUTCOMES

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HMG-CoA reductase inhibitors (statins) are the most prescribed class of drugs in the world. Some authors suggest that positive effects of statins were reported for statins against pneumonia. These positive studies data were counterbalanced by at least one negative prospective cohort study. Where lies the truth? Better understanding the statins influence and their potential role in pathophysiological pneumonia mechanisms is needed because of high quantity of subjects receiving statins with numerous medical conditions significantly associated with increased short-term mortality.

KEY WORDS: statins, pneumonia, outcomes, statin effects

ВПЛИВ ТЕРАПІЇ СТАТИНАМИ НА РЕЗУЛЬТАТИ ЛІКУВАННЯ ПНЕВМОНІЇ

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Інгібітори ГМГ-КоА-редуктази (статини) є класом медикаментів, що призначається найчастіше у світі. Деякі автори в публікаціях відзначають позитивні ефекти терапії статинами у разі захворювання пневмонія. Позитивні дані цих досліджень були врівноважені, принаймні одним негативним результатом у ході проспективного когортного дослідження. Де знаходиться істина? Краще розуміння впливу терапії статинами і їх потенційної ролі в патофізіологічних механізмах захворювання пневмонія необхідно через високу кількість суб'єктів, які отримують статини, з численними захворюваннями, пов'язаними з підвищеною короткостроковій смертності.

КЛЮЧОВІ СЛОВА: статини, пневмонія, результати, ефекти статинів

ВЛИЯНИЕ ТЕРАПИИ СТАТИНАМИ НА ИСХОДЫ ПНЕВМОНИИ

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Ингибиторы ГМГ-КоА-редуктазы (статины) наиболее часто назначаемый класс медикаментов в мире. Некоторые авторы в публикациях отмечают положительные эффекты терапии статинами в случае заболевания пневмония. Позитивные данные этих исследований были уравновешены, по крайней мере одним отрицательным результатом в ходе проспективного когортного исследования. Где находится истина? Лучшее понимание влияния терапии статинами и их потенциальной роли в патофизиологических механизмах заболевания пневмония необходимо из-за высокого количества субъектов, получающих статины с многочисленными заболеваниями, связанными с повышенной краткосрочной смертности.

КЛЮЧЕВЫЕ СЛОВА: статины, пневмония, результаты, эффекты статинов

HMG-CoA reductase inhibitors (statins) are the most prescribed class of drugs in the world as a common chronic treatment because they significantly improve survival in patients with cardiovascular disease and in apparently healthy persons without hyperlipidemia but with elevated C-reactive protein levels [1]. Besides this well-known effect, they are responsible in decreasing of intermediary products of mevalonate synthesis cascade inhibition, including farnesyl pyrophosphate and geranyl

pyrophosphate, which are involved in the activation by isoprenylation of small GTP-binding proteins, which are involved in the pleiotropic effects of statins. These actions result in numerous effects of statins as anti-inflammatory and anti-oxidant, immune modulation, antithrombotic effects, protection of the endothelial function, and activation of vitamin D, decrease in the activity of platelets, an increase in the tissue plasminogen activator and a decrease of its inhibitor, and an enhancement in the expression and functional activity of thrombomodulin, an essential co-factor for protein C activation [2]. The inhibition of mevalonate synthesis by statins leads to a lesser activation of the small GTP-binding proteins, which play a key role in the activation (molecular on/off switches) of intracellular inflammatory signaling pathways. In particular, the activation of nuclear factor kappa B, mitogen-activated protein kinase, and phosphatidylinositol-3 kinase systems by isoprenylated protein kinases is blunted. Therefore, the expression of cytokines, acute phase proteins, chemokines, adhesion molecules, and enzymes is partially inhibited in the presence of statins [3]. For example, the JUPITER study showed that rosuvastatin significantly lowers CRP levels, an independent predictor of future cardiovascular events [4, 5]. Statins influence leucocyte function by a direct inhibition of the major histocompatibility complex type II gene of antigen presenter cells and an allosteric block site of the lymphocyte function-associated antigen [6], which has a significant role in lymphocyte adhesion and activation.

Are statins antibacterials? Japanese microbiologist Akira Endo was first who discovered in the 1970s, during a research for antimicrobial agents, natural products with a powerful inhibitory effect on HMG-CoA reductase in a fermentation broth of Penicillium citrinum, including ML236B (compactin). In spite of this no useful antimicrobial activity has been found in case of HMG-CoA reductase inhibitor previously [7, 8]. Clinical trials data with compactin have never been made public believed due to his serious animal toxicity, that's why lovastatin became the first public known HMG-CoA reductase inhibitor with clinical studies data [9]. Lovastatin in animal and in vitro studies showed inhibition of the bacterial growth of strict intracellular bacteria such as Coxiella burnetii [10]. Researchers believed that it became possible because the genome of these bacteria contains the steroid biosynthesis pathway, and bacterial multiplication is achieved in a vacuole rich in cholesterol [11]. Nowadays, according to a meta-analysis of a number of observational studies patients on statin therapy seemed to have a better outcome of bacterial infections in respiratory tract infection, but the association did not reach statistical significance after adjustment for apparent publication bias OR 0.79 (95 % CI 0.58–1.07). 12 from 15 observational studies on pneumonia and statins, showed association between statin-use and a favorable outcome [12]. In another study, patients, which are receiving statins for prolonged periods also as older patients, may have a higher plasma simvastatin levels compared with healthy volunteers. Some statins, in particular simvastatin, had an antimicrobial effect in vitro but require concentrations that are far higher than are probably achieved in vivo with traditional indications for statins. In this study simvastatin showed an unexpected significant antimicrobial effect against MSSA (Methicillin-sensitive Staphylococcus aureus) (mean MIC 29.2 mg/L) and to a lesser extent against MRSA Methicillin-resistant Staphylococcus aureus) (mean MIC 74.9 mg/L) on bacterial growth and to assess possible synergistic effects with penicillin. The aim of another similar study was determined MIC-values with possible antibacterial effects for simvastatin, fluvastatin and pravastatin against primary pathogens of the respiratory tract (S. pneumoniae, M. catarrhalis and H. influenza) by traditional antibacterial assays. Low Simvastatin concentrations that was detected in human blood during therapy (1–15 nmol/L) and just a single doses of statins was given to healthy volunteers, can explain the fact that improving of antibacterial effects of whole blood was not detected. Contrariwise, as in above mentioned investigations was found that simvastatin at high concentrations 15 μg/mL (36 μmol/L) rapidly kills S. pneumoniae and M. catarrhalis. Statins did not affect growth or viability of H. influenzae. Thus, according to the results of the study, a direct bactericidal

effect of statins in vivo is probably not the mechanism which can explain beneficial effect of statins against various infections [13]. Earlier observed beneficial effect of statins might be explained by potential anti-inflammatory properties [14], also, statins have been reported to inhibit host cell invasion by Staphylococcus aureus [15] as well as to enhance bacterial clearance of this pathogen [16] and also has been proposed a direct antibacterial effect against it [17 - 18]. Recently, statins were shown not only to improve killing of Staphylococcus aureus by phagocytic cells [19]. All in vitro experiments mentioned above have been performed using statin concentrations between 0.1–50 μM, which greatly exceeds the concentrations present in human blood during statin treatment (1–15 nmol/L) [20, 21]. Statin concentrations in these cell experiments were compared with concentrations detected in human plasma.

Positive antimicrobial effect of statins was found not only in case of respiratory pathogens but also in case of periodontal pathogens that have been identified in atheromatous tissue and associated with increased carotid intima media thickness. The main periodontal pathogen. Porphyromanos gingivalis, seem to increases the number of macrophages, T-cells and lipids within the plaques. Increased levels of inflammatory biomarkers such as C-reactive protein (CRP) were found to be predictive of acute events in healthy individuals. Hyperlipidaemic patients were found to be more prone to periodontitis, and statins can be beneficial for periodontal health [22]. Moreover, statins have been shown to protect against pneumococcal infection in a mouse model of sickle cell disease [18] and in vitro to inhibit a number of strains of fungi and the parasite Plasmodium falciparum, but statins concentrations in these experiments were much higher than in serum during statin therapy. Murine models have shown also anti-chlamydial and immunomodulatory effects of simvastatin during infection [23]. Another study showed the antibacterial effect of atorvastatin and rosuvastatin in Gram + and Gram–bacteria [24]. Result of other studies suggest the superiority of the antibacterial effects of atorvastatin or simvastatin to that of rosuvastatin. MSSA, MRSA, vancomycin-susceptible enterococci (VSE), vancomycin-resistant enterococcus (VRE), acinetobacter baumannii, staphylococcus epidermidis, and enterobacter aerogenes, were more sensitive to both atorvastatin, and simvastatin compared to rosuvastatin. On the other hand, escherichia coli, proteus mirabilis, and enterobacter cloacae were more sensitive to atorvastatin compared to both simvastatin and rosuvastatin [25]. Systematic review and meta-analysis of Imad M. Tleyjeh et. (2009), suggest that statin use may be associated with a beneficial effect in treating and preventing different infections. Patients who have infections and are taking statins had a better outcome, including chance of survival: adjusted effect in treating infections was 0.55 (95 % confidence interval, 0.36–0.83; I2 = 76.5 %) in favor of statins. The pooled effect estimate addressed infection prevention was 0.57 (95 % confidence interval, 0.43-0.75; I2 = 82 %) in favor of statin use [26].

Among possible mechanisms of antimicrobial activity can be sort out interference with L-mevalonic acid synthesis, COX-2 modulation, reactive oxygen species suppression. Statins have been shown to lower LDL levels by interfering with mevalonate synthesis with influence pathogen-induced inflammation. Increased COX-2 stability by Atorvastatin, could increase dendritic cell function after infectious bouts with compensation of some adverse effects of sustained inhibition of COX-2. On the other hand, possible involving reduced formation of reactive oxygen species, oxidation of LDL and adhesion of neutrophils, while apoptosis, bacterial phagocytosis and bacterial clearance are unaffected in case of Simvastatin allows to have a protective role in lung inflammation [27]. Experimental studies have shown their effect in the modulation of the cytokine cascade and in the organization of the immunological response to respiratory infection [28]. For example, statin therapy was associated with a reduction in the levels of inflammatory cytokines in patients with acute bacterial infections: TNF-α and IL-6 levels were significantly reduced in the simvastatin group ($p = 0.02$ and $p = 0.02$, respectively), while no such difference was observed in the placebo group [29]. Although it has been

suggested that statins may have an effect in the modulation of the cytokine cascade and on the prognosis of patients with community acquired pneumonia (CAP). However, prospective, randomised, double–blind, placebo–controlled trial data showed that use of simvastatin, 20 mg once daily for 4 days, since hospital admission did not reduce the time to clinical stability and the levels of inflammatory cytokines in hospitalised patients with community-acquired pneumonia [30].

During of the role of statins in community acquired pneumonia, [31] was shown that statins have immunomodulatory, and antioxidative actions, and a significant effect on the concentrations systemic cytokine [23-26]. Linnea A. Polgreen etc. reports data showed that the protective effect of statins against pneumonia among 19,078 (15.3 %) patients that were diagnosed, after surviving for 1 year post- acute myocardial infarction, is most likely the result of non-random treatment assignment (i.e., a healthy-user bias). The statin coefficient -0.016 ($p < 0.001$), indicated that statins therapy was associated with a reduction in pneumonia rate in this category of patients [32]. There have been other three retrospective studies also showed improved outcome in patients taking statins. It was found than statin use is independently protective against increasing of C-reactive protein levels, the value of which failed to decrease by 50 % or more at day 4 (AOR 0.52, 95 % CI: 0.30-0.89, $p = 0.02$). Also in these studies, statins reduced cytokine and other inflammatory markers levels in patients with cardio-vascular pathology, and it was predisposed that the improved outcome in patients with pneumonia happened due to the anti-inflammatory and immunomodulatory effects of the statins. [33]. Other studies showed in-vitro that simvastatin therapy (1μM) can cause restoring of neutrophil migration (preserved chemokinesis) and old neutrophil chemotaxis (directed migration) in patients with pneumonia to baseline values despite the patients older age compared with healthy controls (pneumonia, 1·1 μm/min, $p = 0·02$). 2 weeks of oral simvastatin in healthy volunteers over ≥ 65 years, ($n = 20$) increased the accuracy of neutrophil migration in vitro (MD 1·68 μm/min, $p = 0·02$) replicating in-vitro work. [34]. As prophylaxis or in the very early management, the anti-inflammatory effects of statins may be protective in sepsis, but side effects may prevail as the disease progress with establishing of multiorgan dysfunction. Supratherapeutic plasma levels of statins and their hepatic metabolization in critically ill patients can be translated to an increasing the risk of toxicity. Also metabolization of statins by the cytochrome P450 3A4 system may interfere with other medications commonly used in the Intensive Care Unit (ICU) (i.e., amiodarone, macrolide anti-biotics) [2]. Prior studies suggested a potential survival benefit for statins in severe infections, from patients already receiving the lipid-lowering therapy. E.M. Mortensen etc. [35] found that prior outpatient use of statins was strongly associated with a decreased 30-day mortality for subjects aged over 65 years that were hospitalized with CAP diagnosis and increasing incidence of pneumonia and pneumonia-related mortality. In total, were included 8,652 subjects, among them 18.1 % of subjects were using statins. Adjusting of potential confounders showed, that current statin use (odds ratio (OR) 0.54, 95 % confidence interval (CI) 0.42–0.70) were significantly associated with decreased 30-day mortality. In another large cohort study was found that preadmission statin use was associated with considerably reduced risk of death among ICU patients. The reduced risk of death remained robust in various subgroup analyses, including among new and long-term statin users, no clear association wasn't found between former statin use and non-statin lipid-lowering drug use and risk of death, which supports a causal association between statin use and reduced risk of death among ICU patients [36]. In a 2006 Schmidt and colleagues reported results of German cohort study with 120 ICU patients with multiple organ dysfunction syndrome included, where statin use was associated with substantially reduced in-hospital mortality (MRR = 0.53, 95 % CI = 0.29 to 0.99) [37]. The biological mechanisms underlying this data are not entirely understood still. Some authors decided that strong experimental evidence of beneficial statins effects on platelet function, coagulation, fibrinolysis, plaque formation, and inhibition of endothelial dysfunction [38-43] can decrease the risk of fatal venous

and arterial thrombotic events due to presence of systemic inflammatory response syndrome and/or severe infections in ICU patients [44-46]. Multi-analysis of fourteen studies with 269,739 participants included showed that statin treatment was associated with lower 30-day mortality, with an OR of 0.44 (95 % CI, 0.29-0.67), and an adjusted OR of 0.59 (95 % CI 0.48-0.73, NNT30d = 19). Statin therapy was also associated with lower long-term (> 30 days) mortality, with an OR of 0.49 (95 % CI, 0.29-0.84) and an adjusted OR of 0.65 (95 % CI, 0.51-0.82, NNTlong-term = 15) [47].

These positive studies data need to be counterbalanced by at least one negative prospective cohort study of admitted for treatment of suspected or confirmed infection to hospital wards patients, where the risk of significant clinical deterioration was low, with a 30-day mortality of 5.7 % and ICU admission risk of 3.3 %. Markers of systemic inflammation (CRP, WCC) improved with time but prior statin therapy did not alter the evolution of these inflammatory markers levels. [48]. Sachin Yende et all. [49] in a large, prospective, multicenter cohort study of patients hospitalized with CAP, found no evidence of a protective statins effect on the development of severe sepsis. In this study authors made not only comparison of statins use (in the week before admission) and with no prior use patients groups but also they compared prior statin users with continued inhospital therapy (continued use cohort) with no prior use or no inhospital use group. Were found only modest differences in levels of circulating biomarkers in community-acquired pneumonia, perhaps due to healthy user effects and indication bias. Adjustment of patient's characteristics and propensity for statin use, showed no mortality benefit in prior (odds ratio, 0.90 [0.63–1.29]; p = 0.57) or continued statin use groups (odds ratio, 0.73 [0.47–1.13]; p = 0.15). Further investigations showed that adding a statin to antibiotic therapy didn't lead to survival improvement in critically ill patients with ventilator-associated pneumonia (VAP). Investigation data helped to emphasize that 28-day mortality was higher in case with simvastatin - 22.6 % (95 % confidence interval [CI], 15.7 % - 31.5 %) compared with placebo group - 14.3 % (95 % CI, 8.9 % - 22.2 %, P = 0.06); between-group difference, 8.3 % [95 % CI, − 2.2 % to 18.7 %]). This trial was stopped early for futility underscores that statins should not be employed as adjunctive therapy [50]. Prospective population based cohort study of CAP patients managed in an outpatient setting, was made from 2000–2002, showed that have shown either no association with mortality or increased mortality with the use of these medications in subjects with infectious diseases [51-52]. Meta-analysis of observational studies such as cohort studies and case-control studies of pneumonia inpatients, identified that in this case the raw data demonstrated no significant benefit from statin therapy (OR = 0.86, 95 % CI, 0.56-1.34) [53]. In the Dublin study, statin use appeared to predispose to, rather than protect against pneumonia. In the minimally adjusted model, statin use had a odds ratio of 1.13 (0.95–1.34), while in the fully adjusted model statin use had a odds ratio of 1.26 (1.01–1.56). In 2006 was made big prospectively collected database study on 3415 patients in 6 hospitals observed that confounding due to the "healthy user effect" may be responsible for the observed benefits of statins. No significant association was found, the theory that patients taking statins are also more likely to do other beneficial health behaviors such as taking pneumococcal and influenza vaccination or stopping smoking that may be associated with better outcome [54].

Why have other authors failed to demonstrate a benefit for statins therapy if the previous some studies have shown it? Some authors suggest that positive effects of statins were reported for statins against pneumonia due to the differences in patients group who were treated with statins and those who were not. The biggest part of reports about protective effects of statins against pneumonia and other infections was based on data where treatments are not assigned randomly. In other cases it was maybe the small amount of patients included in the study. Also the result can be affected by the severity of concomitant pathology, personal experience of the patient, administration by family doctor or self-administration of antibiotics drugs before the admission to the department, influence of other medications taken for chronic disease

etc. Better understanding the statins influence and their potential role in pathophysiological CAP mechanisms is the need to since subjects receiving statins have numerous medical conditions significantly associated with increased short-term mortality.

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