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Clinical researches

UDC 616.12-008.315-085.84

FUNCTIONAL CLASS OF CHRONIC HEART FAILURE AND CLINICAL FEATURES OF PATIENTS WITH PERMANENT PACEMAKERS

I. M. Kolomytseva[1], D. E. Volkov[2], D. A. Lopin[2], M. I. Yabluchansky[1]
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The study included 162 patients (89 men and 73 women) aged 69 ± 10 years who underwent permanent pacing about atrio-ventricular block, permanent atrial fibrillation and sick sinus node syndrome 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 functional class (FC) CHF. Patients with pacemakers the most frequent had II and III CHF FC which more often associated with myocardial infarction, stable angina, diabetes mellitus, atrial fibrillation, stage IIA and IIB CHF. It is concluded that patients with ECS require optimization of medical interventions.

KEY WORDS: permanent pacing, chronic heart failure, functional class of chronic heart failure

ФУНКЦІОНАЛЬНИЙ КЛАС ХРОНІЧНОЇ СЕРЦЕВОЇ НЕДОСТАТНОСТІ ТА КЛІНІЧНІ ОСОБЛИВОСТІ ПАЦІЄНТІВ З ПОСТІЙНОЇ ЕЛЕКТРОКАРДІОСТИМУЛЯЦІЄЮ

І .М. Коломицева[1], Д. Є. Волков[2], Д. А. Лопин[2], М. І. Яблучанський[1]
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Обстежені 162 пацієнта (89 чоловіків і 73 жінки) у віці 69 ± 10 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 кардіоресінхронізуючою терапією (CRT- P і CRT- D). Клінічні ознаки пацієнтів оцінювалися в залежності від функціонального класу (ФК) ХСН. У пацієнтів з ЕКС найбільш часто зустрічалися II і III ФК ХСН, з якими найчастіше асоціювалися постінфарктний кардіосклероз, стабільна стенокардія, цукровий діабет, фібриляція передсердь, IIA і IIБ стадії ХСН. Робиться висновок, що пацієнти з ЕКС вимагають оптимізації медикаментозних втручань.

КЛЮЧОВІ СЛОВА: постійна електрокардіостимуляція, хронічна серцева недостатність, функціональний клас хронічної серцевої недостатності

ФУНКЦИОНАЛЬНЫЙ КЛАСС ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ И КЛИНИЧЕСКИЕ ОСОБЕННОСТИ ПАЦИЕНТОВ С ПОСТОЯННОЙ ЭЛЕКТРОКАРДИОСТИМУЛЯЦИЕЙ

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Обследованы 162 пациента (89 мужчин и 73 женщины) в возрасте 69 ± 10 лет, подвергшихся 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 функционального класса (ФК) ХСН. У пациентов с ЭКС наиболее часто

встречались II и III ФК ХСН, с которыми чаще ассоциировались постинфарктный кардиосклероз, стабильная стенокардия, сахарный диабет, фибрилляция предсердий, IIА и IIБ стадии ХСН. Делается вывод, что пациенты с ЭКС требуют оптимизации медикаментозных вмешательств.

КЛЮЧЕВЫЕ СЛОВА: постоянная электрокардиостимуляция, хроническая сердечная недостаточность, функциональный класс хронической сердечной недостаточности

INTRODUCTION

Pacemaker implantation doesn't remove the problem of the therapeutic management of patients [1]. One of the most important clinical syndromes is chronic heart failure (CHF) that requires medical support [2].

The main criterion for the effectiveness of both the pacing and pharmacological interventions for chronic heart failure is a functional class (FC CHF).

At all the urgency of the problem, we haven't found any studies in which patients with clinical features of pacemaker due to FC CHF would have been investigated.

OBJECTIVE

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

MATERIALS AND METHODS

On the basis of the department of ultrasonic and instrumental diagnostics with miniinvasive interventions of SI «Zaytsev V.T. Institute of General and Urgent Surgery NAMS of Ukraine» there were examined 162 patients (89 men and 73 women) aged 69 ± 10 years, who underwent permanent pacing. Among the indications for pacemaker implantation there were atrio-ventricular block (AV block) – 89 patients (55 %), permanent atrial fibrillation (AF) – 25 patients (15 %), sick sinus node syndrome (SSNS) - 32 people (20 %) with pacing modes DDD/DDDR and VVI/VVIR, and chronic heart failure and dilated cardiomyopathy - 16 patients (10 %) with cardiac resynchronization therapy (CRT-P and CRT-D). In the early postimplantation period (3-5 days) medical therapy with angiotensin converting enzyme inhibitors, beta -blockers, calcium channel blockers, antiplatelet agents, anticoagulants of direct action.

There were estimated sex (male, female), age, forms of ischemic heart disease (IHD) – postinfarction cardiosclerosis and stable angina (FC I, II, III and IV), arterial hypertension (AH) – stages I, II, III and degrees 1, 2, 3, diabetes mellitus (DM) – types I and II, atrial fibrillation (AF) – permanent, persistent or paroxysmal, initially identified and long-term persistent and CHF stages – I, IIA, IIB and III. Depending on the clinical symptoms, patients were divided into 4 groups – FC I, II, III and IV CHF. To determine the FC CHF there were used guidelines of the Ukrainian Association of Cardiology (2012) [3].

Evaluation was made of the incidence of clinical features in patients with pacemaker and FC CHF 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 nonparametric U - Mann -Whitney 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 FC CHF**.**

In all groups FC CHF, the average age of patients was not significantly different ($p > 0,05$). The oldest were in the group FC II CHF, and the younger ones – in groups FC I and III CHF.

In subgroups of men and women highest number of patients was in group FC II CHF. Rarely in both groups patients with FC I and III CHF was found. The least number of patients in the subgroups of men and women was found in the group FC IV CHF.

In patients with postinfarction cardiosclerosis and stable angina most often FC II CHF was found. The least number of patients in these subgroups were in the group FC IV CHF. In contrast to the subgroup of stable angina, in the subgroup with postinfarction cardiosclerosis patients with FC I CHF were absent.

Table

Clinical features of patients with cardiac pacemakers

Clinical data			Total	FC CHF			
				FC I	FC II	FC III	FC IV
Age, years (M ± sd)			162	69 ± 10	70 ± 11	69 ± 8	66 ± 10
Sex (n,% ± sp)		Male	89	7 (8 ± 3)	41(46 ± 5)	39 (44 ± 5)	2 (2 ± 1)
		Female	73	12 (16 ± 4)	40 (55 ± 6)	15 (21 ± 5)	6 (8 ± 3)
IHD (n,% ± sp)	Postinfarction cardiosclerosis		27	-	18 (67 ± 9)	8 (29 ± 9)	1 (4 ± 4)
	Stable angina	Total	56	6 (11 ± 4)	24 (43 ± 7)	22 (39 ± 7)	4 (7 ± 3)
		FC I	15	1 (7 ± 7)	9 (60 ± 13)	4 (26 ± 11)	1 (7 ± 7)
		FC II	24	2 (8 ± 6)	9 (37 ± 10)	10 (42 ± 10)	3 (13 ± 7)
		FC III	14	3 (21 ± 10)	5 (36 ± 13)	6 (43 ± 13)	-
		FC IV	3	-	1 (33 ± 27)	2 (67 ± 27)	-
AH (n,% ± sp)	Total		142	18 (13 ± 3)	76 (53 ± 4)	41 (29 ± 4)	7 (5 ± 2)
	Stage	I	4	2 (50 ± 25)	1 (25 ± 22)	1 (25 ± 22)	-
		II	86	14 (16 ± 4)	45 (52 ± 5)	25 (29 ± 5)	2 (3 ± 2)
		III	52	2 (4 ± 3)	30 (58 ± 7)	15 (29 ± 6)	5 (9 ± 4)
	Degree	1	52	8 (15 ± 5)	24 (46 ± 7)	17 (33 ± 7)	3 (6 ± 3)
		2	62	9 (14 ± 4)	36 (58 ± 6)	14 (23 ± 5)	3 (5 ± 3)
		3	28	1 (4 ± 4)	16 (57 ± 9)	10 (35 ± 9)	1 (4 ± 4)
DM (n,% ± sp)	Type	I	-	-	-	-	-
		II	26	3 (12 ± 6)	17 (65 ± 9)	5 (19 ± 8)	1 (4 ± 4)
AF (n,% ± sp)	Total		55	9 (16 ± 5)	21 (38 ± 7)	25 (46 ± 7)	-
	Paroxysmal and persistent		25	6 (24 ± 9)	11 (44 ± 10)	8 (32 ± 9)	-
	Permanent		25	3 (12 ± 6)	9 (36 ± 10)	13 (52 ± 10)	-
	Initially identified		2	-	1 (50 ± 35)	1 (50 ± 35)	-
	Long-term persistent		3	-	-	3 (100 ± 0)	-
CHF stage (n,% ± sp)	Total		162	19 (12 ± 3)	81 (50 ± 4)	54 (33 ± 4)	8 (5 ± 2)
	I		20	14 (70 ± 10)	6 (30 ± 10)	-	-
	IIA		93	4 (4 ± 2)	67 (72 ± 5)	21 (23 ± 4)	1 (1 ± 1)
	IIB		47	1 (2 ± 2)	8 (17 ± 5)	33 (70 ± 7)	5 (11 ±5)
	III		2	-	-	-	2 (100 ± 0)

Legend: * p<0,05, ** p<0,01- in current values between groups.

In the subgroups of patients with the FC II, III and IV of stable angina there observed the highest number of patients with FC III CHF. In the subgroup of FC I highest number of stable angina patients was observed in group FC II CHF, rarely patients with FC III CHF was found. In subgroups FC II and III of stable angina the fewest number of patients was in group FC I CHF, in the subgroup with FC I of stable angina the fewest number of patients was in groups FC I and IV CHF. In contrast to the subgroups FC I and II of stable angina, in the subgroup FC III and IV of stable angina patients with FC IV CHF were absent, while in the subgroup FC IV of stable angina patients with FC I CHF were also absent.

Among patients with hypertension there were observed the largest number of patients in group FC II CHF. The least of all patients was in group FC IV CHF. The greatest number of patients in the subgroup with stage I hypertension were observed in group with FC I CHF, in subgroups with stages II and III hypertension – in groups with FC II CHF. The least number of patients in selected subgroups of stages hypertension occurred in different groups of FC CHF: so, in the subgroup with stage I hypertension there was the least of all patients in group FC II and III CHF, in the subgroup with stage II hypertension – in group with FC IV CHF, in the subgroup with stage III hypertension – in group with FC I CHF. In the subgroup with stage I hypertension patients with FC IV CHF were absent. In selected subgroups degrees 1, 2 and 3 of hypertension were the highest number of patients in group with FC II CHF. The fewest number of patients in subgroups 1 and 2 degrees of hypertension

were observed in group FC IV CHF, and in the subgroup degree 3 of hypertension the fewest number was in groups FC I and IV CHF.

Patients in the subgroup with type I diabetes were absent. Among patients with type II diabetes the most frequent was found in group FC II CHF. The least number of patients in this subgroup was observed in the group FC IV CHF.

Among patients with AF the most frequent there were found patients in group CHF FC III. The least number of patients observed in group with FC I CHF. In group FC IV CHF patients were absent. The greatest number of patients with paroxysmal and persistent AF was observed in group FC II CHF, with permanent AF – in group FC III CHF. The least number of patients with paroxysmal and persistent, as well as with permanent AF was observed in group FC I CHF. In the subgroup with initially identified there was observed an equal number of patients in group FC II and III CHF and in group FC I CHF patients were absent. In the subgroup with long-term persistent AF patients were observed only in FC III CHF.

In the subgroup of patients with CHF the most frequent patients with FC II CHF were found. The least of all patients in this subgroup was observed in the group with FC IV CHF. The greatest number of patients in selected subgroups of stages CHF occurred in different groups of FC CHF: in subgroup of stage I CHF the most frequent patients in group FC I CHF were found, in the subgroup of stage IIA CHF – in group FCII CHF, in subgroup of stage IIB CHF – in group FC III CHF, in the subgroup of stage III CHF patients were found only in group FC IV CHF. The least number of patients also occurred in different groups FC CHF: in subgroup of stage I CHF there were observed in the group FC II CHF, in the subgroup of stage IIA CHF – in group FC IV CHF, in a subgroup of stage IIB CHF – in group FC I CHF. In the subgroup of stage I CHF patients in the group FC III and IV CHF were absent.

Data [1, 4, 5, 6] about the importance of assessing the impact of FC CHF in permanent pacing and medical support are confirmed in our study. Our data on higher FC CHF in patients with atrial fibrillation and implantable pacemaker indirectly correspond to the data [7, 8] for its constant and [9] - persistent forms.

Our data about the frequency of postinfarction cardiosclerosis, arterial hypertension and diabetes mellitus in patients with implanted pacemaker in different FC CHF weren't found in the literature and are the new ones.

Significant frequency of occurrence and relations of high CHF FC with studied clinical features of patients with implanted pacemaker shows the need for optimization of their medical treatment.

CONCLUSIONS

1) Patients with a permanent pacemaker were found the most frequently with FC II and III CHF, which often associated with myocardial infarction, stable angina, diabetes mellitus, atrial fibrillation, stage IIA and IIB CHF.

2) The high frequency of FC II and III CHF occurrence in patients with permanent pacing requires optimization medical interventions.

PROSPECTS FOR FUTURE STUDIES

It seems to be reasonable to study medical optimization of chronic heart failure in clinical features of patients with permanent pacemaker.

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IMPLEMENTATION OF BIOFEEDBACK IN A CLOSED LOOP OF HEART RATE VARIABILITY AND PACED BREATHING IN PATIENTS WITH ARTERIAL HYPERTENSION

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The effectiveness of biofeedback in a closed loop of heart rate variability (HRV) and paced breathing in patients with arterial hypertension was studied. 61 subjects with arterial hypertension (31 females and 30 males, mean age 56.8 ± 6.2 years) were examined. In accordance with the objective of the study all subjects were divided into 2 groups: 1 - biofeedback group (34 subjects) and 2 - the comparison group (27 subjects). 5 biofeedback sessions were performed in biofeedback group. In the comparison group only two biofeedback sessions were performed - at admission and before discharge from the hospital. Efficacy of biofeedback was evaluated by comparing the values of systolic and diastolic blood pressure (SBP and DBP, respectively), heart rate (HR), HRV indices, indicators of optimality (O), sensitivity (S) and efficiency (E) and BQI index at admission and discharge in both groups of patients. The use of biofeedback in arterial hypertension subjects allowed to achieve better control of heart rate, systolic and diastolic blood pressure and improves HRV indices. The positive dynamics of optimality and the integral BQI values indicated a training effect of regulation systems.

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

ЗАСТОСУВАННЯ БІОЛОГІЧНОГО ЗВОРОТНОГО ЗВ'ЯЗКУ В ЗАМКНУТОМУ КОНТУРІ ВАРІАБЕЛЬНОСТІ СЕРЦЕВОГО РИТМУ І МЕТРОНОМІЗОВАНОГО ДИХАННЯ У ПАЦІЄНТІВ З АРТЕРІАЛЬНОЮ ГІПЕРТЕНЗІЄЮ

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Для вивчення ефективності біологічного зворотного зв'язку в замкнутому контурі варіабельності серцевого ритму (ВСР) і метрономізованого дихання у пацієнтів з артеріальною гіпертензією був обстежений 61 пацієнт з артеріальною гіпертензією (31 жінка і 30 чоловіків, середній вік 56,8 ± 6,2 років). У відповідності з метою дослідження всі випробувані були розділені на 2 групи: 1 - група біофідбеку (34 пацієнтів) та 2 - група порівняння (27 пацієнтів). У групі біофідбеку було проведено 5 сеансів біологічного зворотного зв'язку. У групі порівняння були виконані тільки два сеанси – при надходженні до лікарні та перед випискою. Ефективність біологічного зворотного зв'язку оцінювали шляхом порівняння значень систолічного і діастолічного артеріального тиску, частоти серцевих скорочень, індексів ВСР, показників оптимальності (О), чутливості (S), ефективності (Е) та інтегральним індексом біофідбеку BQI, при надходженні до лікарні та перед випискою в обох групах пацієнтів. Використання біологічного зворотного зв'язку у пацієнтів з артеріальною гіпертензією дозволяє досягти кращого контролю частоти серцевих скорочень, систолічного і діастолічного артеріального тиску та поліпшення показників ВСР. Позитивна динаміка оптимальності та BQI, що спостерігалася, вказує на ефект тренування систем регуляції.

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

ПРИМЕНЕНИЕ БИОЛОГИЧЕСКОЙ ОБРАТНОЙ СВЯЗИ В ЗАМКНУТОМ КОНТУРЕ ВАРИАБЕЛЬНОСТИ СЕРДЕЧНОГО РИТМА И МЕТРОНОМИЗИРОВАННОГО ДЫХАНИЯ У ПАЦИЕНТОВ С АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ

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Для изучения эффективность биологической обратной связи в замкнутом контуре вариабельности сердечного ритма (ВСР) и метрономизированного дыхания у больных с артериальной гипертензией был обследован 61 пациент с артериальной гипертензией (31 женщина и 30 мужчин, средний возраст 56,8 ± 6,2 лет). В соответствии с целью исследования все испытуемые были разделены на 2 группы: 1 – группа биофидбека (34 пациентов) и 2 - группа сравнения (27 пациентов). В группе биофидбека было проведено 5 сеансов биологической обратной связи. В группе сравнения были выполнены только два сеанса - при поступлении в больницу и перед выпиской. Эффективность биологической обратной связи оценивали путем сравнения значений систолического и диастолического артериального давления, частоты сердечных сокращений, индексов ВСР, показателей оптимальности (О), чувствительности (S), эффективности (Е) и интегральному индексу биофидбека BQI, при поступлении и выписке в обеих группах пациентов. Использование биологической обратной связи у пациентов с артериальной гипертензией позволило добиться лучшего контроля частоты сердечных сокращений, систолического и диастолического артериального давления и улучшить показатели ВСР. Положительная динамика оптимальности и BQI указывает на эффект тренировки систем регуляции.

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

INTRODUCTION

Maintaining achieved target blood pressure (BP) levels in patients with arterial hypertension (AH) continues to represent an urgent problem [1].

The desire to minimize the drugs usage in AH treatment boosted searching for non-drug methods. One of them is biofeedback (BFB), its various versions have been used successfully not only in cardiology but also in other branches of medicine [2-5]. A novel approach in BFB is using of heart rate variability (HRV) and the controlled paced breathing (PB) contours [6].

Since the effectiveness of biofeedback with HRV and PB contour in arterial hypertension has not been previously investigated, we decided to perform that research.

The research was conducted under performed under the SRP of the V.N. Karazin Kharkiv National University «Research and development of heart rate variability automatic control system», registration № 0109U000622.

OBJECTIVE

To study the effectiveness of biofeedback in a closed loop of heart rate variability and paced breathing in patients with arterial hypertension.

MATERIALS AND METHODS

61 subjects with arterial hypertension (31 females and 30 males, mean age 56.8 ± 6.2 years) were examined.

Inclusion criteria used were: arterial hypertension I-III stages, 1-3 severiry grades with stable angina pectoris (SAP) I-III functional classes (FC) and chronic heart failure (CHF) I-III functional classes I-IIA stages.

Exclusion criteria were: acute myocardial infarction, SAP FC IV, CHF IV FC, IIB-III stages, acquired valvular defects, implanted pacemakers, atrioventricular conduction disorders, endocrine disorders (diabetes, thyroid diseases), gastric and/or duodenal ulcer in the acute phase.

BP was measured by Korotkov method with Microlife BP AG1- 20 tonometer.

Biofeedback sessions were performed on a computer diagnostic complex «CardioLab 2009» («XAI-Medica») with additional custom module «Biofeedback», including software related audible and visual breathing metronome and dynamic algorithm for determining the current value of HRV indices, changed under PB influence.

HRV parameters were determined in a sliding 1 minute buffer by dynamic spectral decomposition of RR-intervals sequence in monitor ECG recordings using a fast Fourier transform. ECG recordings were performed in the first standard lead with a 1000 Hz signal sampling rate. The calculations were made in real time within the 7 minute session [6]. HRV indices used were: total spectral power (TP) and calculated power of low frequency VLF (V, to 0.05 Hz), mainly associated with humoral regulators and the sympathetic component of the autonomic nervous system; midrange LF (L, 0.05-0.15 Hz), mainly related to the sympathetic and parasympathetic autonomic balance and high frequency HF (H, 0.15-0.40 Hz), mainly related to the parasympathetic autonomic nervous regulation [7]. Further, these parameters have been

converted into two-dimensional coordinate plane with L/H and V/(L+H) axes, corresponding to sympatho-humoral and humoral-vegetative regulation links. As a zero point for these axes the physiological optimum of these balances were selected for each test in accordance with [7], allowing the distance (D) estimation between the current and the optimal values for every subject's HRV indices.

The study algorithm was used to start with a free breath. This step (algorithm initialization) duration was two minutes. On the third minute sympatho-humoral to humoral-vegetative ratio was calculated ratios and representation of paced breath frequency G took place, moving the subjects'maximum of L/H and V/(L+H) current values to the physiological optimum zone, changing a audio-visual metronome rate. The respiration rate G proposed to subject could vary from 6 to 15 breaths per minute.

In accordance with the objective of the study all subjects were divided into 2 groups: 1 - biofeedback group (34 subjects) and 2 - the comparison group (27 subjects). 5 biofeedback sessions were performed in biofeedback group. In the comparison group only two biofeedback sessions were performed - at admission and before discharge from the hospital.

The degree of regulatory systems optimization was assessed in terms of optimality (O), sensitivity (S) and efficiency (E) as a whole and for each of the coordinates of its phase space, as well as the integral indicator " biofeedback quality index» (BQI), covering all changes in biofeedback quality. Methodology for calculating O, S, E and BQI is described in previous publication [6].

All patients received the same treatment in accordance with the Ukrainian Association of Cardiologists Guidelines for arterial hypertension prevention and treatment. [8]. Diuretics, ACE inhibitors, calcium antagonists, beta-blockers were used. Patients with stable angina pectoris were additionally given acetylsalicylic acid and statins, if necessary.

Efficacy of biofeedback was evaluated by comparing the values of systolic and diastolic blood pressure (SBP and DBP, respectively), heart rate (HR), HRV indices, indicators of optimality (O), sensitivity (S) and efficiency (E) and BQI index at admission and discharge in both groups of patients.

The obtained data for all patients was entered into Microsoft Excel, followed by the calculation of mean (M) values and standard deviation (sd). The frequency of the attributes studied, were stated as a percentage, and the average error percentage (Sp) was calculated [9]. The significance of differences between groups on the stages of the study was determined using the U-Mann-Whitney test [10]. The significance of differences between the values of the indices at given stage and before treatment was determined using the T- Wilcoxon test [10].

RESULTS AND DISCUSSION

A clinical characteristic of the subjects in both groups is presented in tab. 1, giving information about most important features of the groups. It can be seen that groups are comparable by clinical features.

Mean SBP, DBP and heart rate values in biofeedback and comparison groups at admission and before discharge are presented in tab. 2. During the same treatment in both groups systemic biofeedback implementation contributed to lower values aforementioned indices.

Values of heart rate variability indices in biofeedback and comparison groups at admission and before discharge are shown in tab. 3. Initially in biofeedback group HRV indices were lower. HRV indices increasing were registered before discharge in both groups, but the biofeedback group had higher values compared to the comparison group.

Optimality, sensitivity and efficiency values measured by the distance from the physiological optimum zone (O^D, S^D and S^D, respectively) in the biofeedback and comparison groups at admission and before discharge are shown in tab. 4. Systematic biofeedback sessions contributed to higher values of optimality due to the effect of the regulation systems «training».

Changes of BQI in biofeedback and comparison groups during the hospital admission are shown in fig. Systematic biofeedback sessions in the biofeedback group contributed its natural approximation to the optimal level, whereas in the control group it remained at the same level.

Table 1

Clinical characteristics of subjects in groups, (n, (% ± *Sp*))

Indices		Group	
		Biofeedback (34)	Comparision (27)
Sex	Males	15, (41.6 ± 8.3)	15, (55.6 ± 9.7)
	Females	19, (52.7 ± 8.4)	12, (44.4 ± 9.7)
Age, years (M ± sd)		54.0 ± 7.6	56.8 ± 6.2
AH stage	I	3, (8.3 ± 4.7)	2, (7.4 ± 5.1)
	II	21, (58.3 ± 8.3)	23, (85.2 ± 6.7)
	III	12, (33.3 ± 8.0)	2, (7.4 ± 5.1)
AH severity grade	Mild	2, (5.5 ± 3.9)	2, (7.4 ± 5.1)
	Moderate	16, (44.4 ± 8.4)	15, (55.6 ± 9.7)
	Severe	9, (25.0 ± 7.3)	10, (37.0 ± 9.5)
SAP FC	I	-	1, (3.7 ± 3.7)
	II	4, (11.1 ± 5.3)	4, (14.8 ± 7.0)
	III	3, (8.3 ± 4.7)	3, (11.1 ± 6.2)
CHF FC	I	14, (38.8 ± 8.2)	16, (59.3 ± 9.6)
	II	2, (5.5 ± 3.9)	5, (18.5 ± 7.6)
	III	-	-
CHF stage	0	11 (30.5 ± 7.8)	3, (11.1 ± 6.2)
	1	11 (30.5 ± 7.8)	14, (51.8 ± 9.8)
	2A	1 (2.8 ± 2.8)	3, (11.1 ± 6.2)
	2B	1 (2.8 ± 2.8)	-

Note: * - P>0.05 between groups.

Table 2

Mean SBP, DBP and heart rate values in biofeedback and comparison groups at admission and at discharge, (M ± sd)

Parameter	Group			
	Biofeedback		Comparision	
	Admission	Discharge	Admission	Discharge
SBP	153.7 ± 17.3*	130.2 ± 11.6*†	158.4 ± 15.7*	133.5 ± 12.7*†
DBP	94.8 ± 13.3*	84.2 ± 8.9*†	94.6 ± 10.3*	85.6 ± 9.9*†
HR	73.2 ± 12.7*	70.1 ± 17.3*†	75.1 ± 9.6*	70.3 ± 8.7*†

Notes: * - p > 0.05 for given index on current stage between groups; † - p > 0.05 for given index in current group comparing to admission levels.

Table 3

Values of heart rate variability indices in biofeedback and comparision groups at admission and before discharge, (M ± sd)

Index	Group			
	Biofeedback		Comparision	
	Admission	Discharge	Admission	Discharge
TP, мс^2	639.9 ± 352.3	2389.7 ± 1160.4†	1003.4 ± 854.5	2067.3 ± 899.7†
VLF, мс^2	257.9 ± 142.1	1117.9 ± 964.6	435.5 ± 370.7	874.3 ± 541.5
LF, мс^2	283.8 ± 363.0	700.0 ± 406.7	290.9 ± 308.2	554.0 ± 327.3
HF, мс^2	189.8 ± 162.1	441.9 ± 203.9	250.1 ± 249.4	567.0 ± 445.6
LF/HF	1.71 ± 1.77	1.57 ± 0.69	2.17 ± 1.86	1.60 ± 1.82

Note: † - p> 0.05 for given index in current group comparing to admission levels.

Table 4

Average O^D, S^D and S^D values in biofeedback and comparison groups at admission and before discharge, (M ± sd)

Index	Group			
	Biofeedback		Comparision	
	Admission	Discharge	Admission	Discharge
O^D	-3.2 ± 4.4*	-6.2 ± 6.9*†	-5.8 ± 7.7*	-6.1 ± 8.1*†
S^D	1.0 ± 0.5*	1.0 ± 0.4*†	0.9 ± 0.5*	0.9 ± 0.5*†
E^D	0.2 ± 0.3*	0.06 ± 0.1*†	0.2 ± 0.2*	0.2 ± 0.3*†

Notes: * - p > 0.05 for given index on current stage between groups; † - p > 0.05 for given index in current group comparing to admission levels.

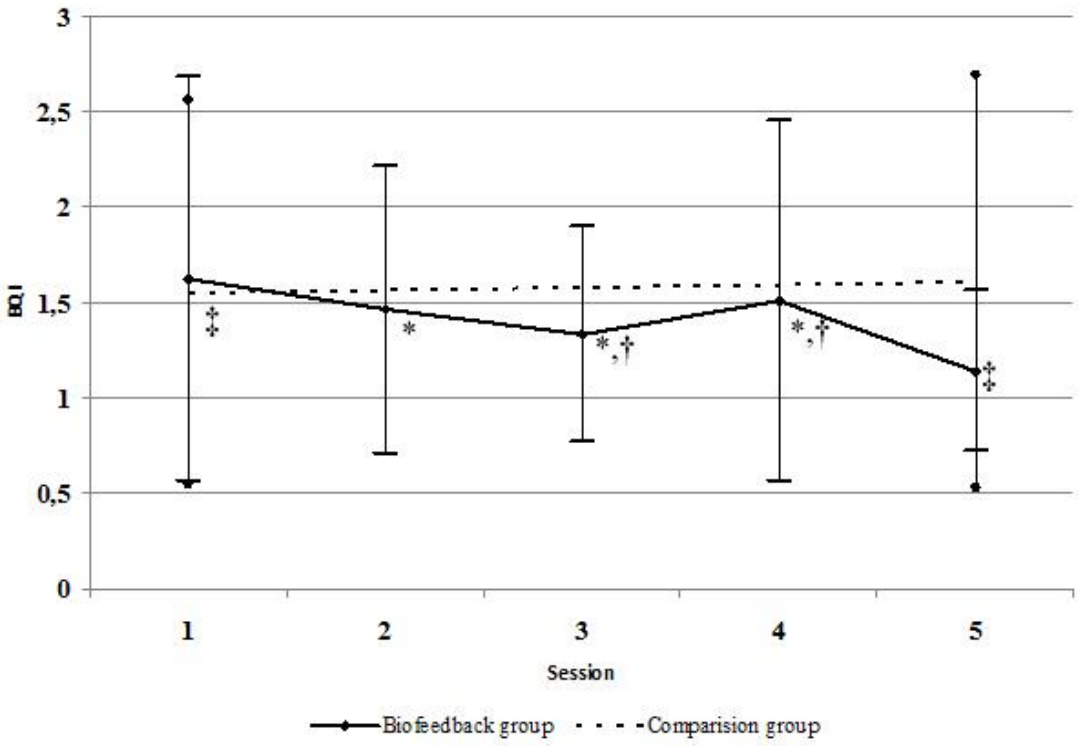

Fig. BQI changes during hospital admission in biofeedback and comparison groups

Note: * - p > 0.05 on current stage comparing to admission values;
† - p > 0.05 on current stage comparing to previous session value;
‡ - p > 0.05 between biofeedback and comparison groups on current session.

The findings suggest that the biofeedback with HRV and PB contour in arterial hypertension subjects not only improves the quality of its control, but also helps to optimize the regulatory systems that are crucial in the mechanisms of the disease [11, 12]. The similar results have been obtained; where it was shown that HRV biofeedback decreases blood pressure in prehypertensive subjects [13] and that the breathing pattern of 5.5 breaths per minute with an inhale/exhale ratio of 5/5 achieved greater HRV than the other breathing patterns [14]. The major difference is that in our study breath rate could be automatically shifted from 6 to 15 breaths per minute «on fly» depending on HRV indices, while almost in all biofeedback studies with paced breathing the breath rate is limited to 6 per minute.

CONCLUSIONS

1) The use of biofeedback with HRV and PB contour in arterial hypertension subjects allows achieving better control of heart rate, systolic and diastolic blood pressure and improves HRV indices.

2) The positive dynamics of optimality and the integral BQI values observed during study demonstrated a high effectiveness of bio-feedback in a closed loop of heart rate variability and paced breathing in patients with arterial hypertension.

PROSPECTS FOR FUTURE STUDIES

The demonstrated effectiveness of proposed new biofeedback in a closed loop of heart rate variability and paced breathing have shown that it can be used in health care practices in hospitals and out-patient clinics.

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PROPHYLAXIS AND THERAPY OF IMPAIRED GLUCOSE TOLERANCE IN LONG-TERM THERAPY OF THE PATIENTS WITH SEVERE DERMATOSES WITH GLUCOCORTICOSTEROID HORMONES

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Impaired glucose tolerance (IGT) is the most wide-spread complication of long-term therapy of severe dermatoses with glucocorticoid hormones among possible steroid-induced disturbances of carbohydrate metabolism being also a component part of the conception « state prior to the development of diabetes». The mentioned complication leads to the development of cardiovascular pathology which in its turn worsens both the general state of the patient and aggravates the dermatosis course. In this connection the work on prophylaxis and therapy of steroid-induced IGT with metformin preparation having a number of therapeutic effects on human organism besides main hypoglycemic activity in patients with skin diseases was carried out.

KEY WORDS: severe dermatoses, protracted, glucocorticosteroid hormones, impaired glucose tolerance, cardio-vascular system, prophylaxis, therapy, metformin

ПРОФІЛАКТИКА ТА ЛІКУВАННЯ ПОРУШЕНОЇ ТОЛЕРАНТНОСТІ ДО ГЛЮКОЗИ У ХВОРИХ НА ТЯЖКІ ДЕРМАТОЗИ ПРИ ДОВГОТРИВАЛІЙ ТЕРАПІЇ ГЛЮКОКОРТИКОСТЕРОЇДНИМИ ГОРМОНАМИ

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Порушена толерантність до глюкози (ПТГ) є найбільш поширеним ускладненням довготривалої терапії глюкокотикостероїдними гормонами тяжких дерматозів серед можливих стероїд-індукованих порушень вуглеводного обміну і також є складовою частиною поняття «переддіабет». Це ускладнення призводить до розвитку патології серцево-судинної системи, що, в свою чергу, погіршує як загальний стан пацієнта так і перебіг дерматоза. У зв'язку з цим була проведена робота по профілактиці та лікуванню стероїд-індукованої ПТГ у хворих на тяжкі шкірні захворювання препаратом метформін, який крім основної цукрознижуючої дії має ще ряд лікувальних ефектів на організм людини.

КЛЮЧОВІ СЛОВА: тяжкі дерматози, довготривала терапія, глюкокортикостероїдні гормони, порушена толерантність до глюкози, серцево-судинна система, профілактика, лікування, метформін

ПРОФИЛАКТИКА И ЛЕЧЕНИЕ НАРУШЕННОЙ ТОЛЕРАНТНОСТИ К ГЛЮКОЗЕ У БОЛЬНЫХ ТЯЖЕЛЫМИ ДЕРМАТОЗАМИ ПРИ ДЛИТЕЛЬНОЙ ТЕРАПИИ ТЯЖЕЛЫХ ДЕРМАТОЗОВ ГЛЮКОКОРТИКОСТЕРОИДНЫМИ ГОРМОНАМИ

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Нарушенная толерантность к глюкозе (НТГ) является наиболее распространенным осложнением длительной терапии глюкокортикостероидными гормонами тяжелых дерматозов среди возможных стероид-индуцированных нарушений углеводного обмена и также является составной частью понятия «преддиабет». Данное осложнение приводит к развитию патологии сердечно-сосудистой системы, что, в свою очередь, ухудшает как общее состояние пациента, так и усугубляет течение дерматоза. В связи с этим была проведена работа по профилактике и лечению стероид-индуцированной НТГ у больных тяжелыми кожными заболеваниями препаратом метформин, который помимо основного сахароснижающего действия обладает еще рядом лечебных эффектов на организм человека.

КЛЮЧЕВЫЕ СЛОВА: тяжелые дерматозы, длительная терапия, глюкокортикостероидные гормоны, нарушенная толерантность к глюкозе, сердечно-сосудистая система, профилактика, лечение, метформин

INTRODUCTION

The main aim of patients with severe wide-spread dermatoses treatment is the improvement of the quality of life of the patients at the expense of exacerbation prevention, normal skin function ensuring, normal level of physical activity maintenance, side effect of medications used in therapy expulsion. On the assumption of the leading role of autoimmune processes and inflammation in severe dermatoses pathogenesis therapy foresees the use of immune modulating and anti-inflammatory medications the most effective of which are the glucocorticosteroid hormones (GCs) [1-3], though the long-term taking of the medication from the mentioned group not only provides the curative effect but also disturbs the state of carbohydrate metabolism, particularly causes the development of impaired glucose tolerance (IGT) [3-6]. In the basis of GCs induced IGT the insulin resistance underlies, which is compensated by excess insulin production for a long time and as a result of that the level of glucose in blood remains normal. Though afterwards under insulin resistance growth, the secretory function of ß-cells weakens [6-7]. The clinical manifestation of early phase of insulin secretion disturbance is the development of postprandial hyperglycemia, i.e. impaired glucose tolerance. IGT is the component part of conception «state prior to the development of diabetes», connecting IGT and impaired fasting glucose (IFG). It was stated that the risk of cardio-vascular complications growth is observed already at the stage prior to the development of diabetes and postprandial hyperglycemia (blood plasma glucose level after eating), is an independent risk factor of cardio-vascular complications development and premature death [7-8]. Funagata Diabetes Study also showed that heightened risk of cardio-vascular complications is connected not with IFG, but with IGT development.

Consequently in connection with the mentioned above the treatment must be conducted on the stage of IGT and IFG, preventing the development of the 2nd type diabetes mellitus [9]. It became the ground for the therapeutic and prophylactic method working out of the GCs induced IGT of the patients with severe dermatoses on long-term therapy by GCs on the basis of dermatology department of SE «Institute of dermatology and venereology of the NAMS of Ukraine».

OBJECTIVE

The purpose of the study is to work out prophylaxis and treatment method of impaired glucose tolerance in patients with severe dermatoses on long-term therapy with gluco-corticosteroids.

MATERIALS AND METHODS

72 patients with severe dermatoses were examined: 39 women, 33 men at the age from 35 to 72 years old, among which 21 patients with severe forms of psoriasis, 20 – with true pemphigus, 10 – with erythema multiforme, 1 – with cicatricial pemphigoid, 8 – with chronic eczema, 9 – with vasculitis, 3 – with dermatitis herpetiformis who took GCs from 0,5 to 5 years and more in a dose 5-60 mg per day according to prednisolone (tab. 1).

Table 1

Distribution of the patients according to the forms of dermatoses and duration of systemic glucocrticosteroids taking

Duration of GCs taking	Severe forms of psoriasis	True pemphigus	Erythema multiforme	Vasculitis	Chronic eczema	Dermatitis herpetiformis	Cicatricial pemphigoid
less than 0,5 years	13	7	6	5	6	2	-
up to 1 year	3	8	3	3	2	1	-
up to 5 years	3	3	1	1	-	-	-
more than 5 years	2	2	-	-	-	-	1

For detection of IGT the oral glucosetolerant test (OGTT) was conducted in all patients. Only the patients with the normal indexes of glucose content in serum according to the biochemical blood examination took part in the trial. The participants of the examination took food ration with not more than 250 grams of carbohydtates per day for three days (but not less than 1,75/kg). Blood sampling from the finger on an empty stomach (minimally 12 hours of starvation) was done (the patients excluded the use of alcohol and intense physical loading for 24 hours before the examination). After that they were given the solution (75 g of glucose dissolved in 250 ml of warm water), which they drank during 3-5 minutes. The second blood sampling was done 120 minutes after glucose solution taking (during this period the patient was calmly sitting, not eating, drinking and smoking).

Results of OGTT interpretation:

- Normal tolerance to glucose is characterized by the glycemia level of less than 8 millimoles per liter (< 140 mg/dl) 2 hours after glucose taking;
- Increase of glucose concentration in blood plasma 2 hours after glucose solution taking more than for 7,8 millimoles per liter (> 140 mg/dl), but less than 11,1 millimoles per liter (< 200mg/dl), testifies for impaired glucose tolerance [10-11].

On the basis of the trial with the aim of IGT revealing patients were subdivided into 2 groups. In the first group there were 31 persons in which IGT was revealed on the long-term GCs therapy. In the second group there were 41 patients who showed no disturbances from the side of carbohydrate metabolism before GCs prescription. With the aim of IGT treatment (I group patients) metformin was prescribed in a dose from 500 to 2000 mg per day depending on susceptibility and effectiveness of the preparation during GCs taking. With the aim of IGT development prophylaxis (II group patients) the preparation was prescribed in a dose 500 mg per day simultaneously with the beginning of GCs taking. The control of medication effectiveness was carried out in both groups one month after its prescription. In diseases demanding lifelong GCs taking, metformin was prescribed in interrupted courses of 1-2 months 3-4 times a year. All the patients receiving GCs during the whole course of the main disease therapy kept diet № 9 according to Pevsner.

Metformin is a peroral hypoglycemic medication from the group of biguanides being the first-line remedy in diabetes mellitus of the 2^{nd} type therapy. Sensitivity of periphery tissues to insulin increases under the effect of metformin. The preparation decreases the glucose production by liver on account of liver sensitivity increase to insulin, decrease of gluconeogenesis and glycogenolysis, what leads to decrease of fasting glucose level. Besides angioprotector activity of the medication is its additional privilege because of which it is very useful in case of coronary artery disease [9, 12-13].

Statistical analysis was conducted on each subject by the «Microsoft Excel 2003» program. The arithmetic mean value (M), standard deviation (sd), the error in determining the arithmetic mean indexes (m) were calculated, the authenticity of differences (p) of comparative group averages were determined using the Student-Fisher t-criterion [14].

RESULTS AND DISCUSSION

In estimation of glucose level in blood serum before the beginning of therapy (prescription of systemic GCs) in the I group 120 minutes after glucose solution taking (75 g) the reliable increase of its level in blood was stated: 7,9 ± 0,1 millimoles per liter. In the II group no impaired glucose tolerance was found at examination: 4,7 ± 0,5 millimoles per liter. After metformin prescription while OGTT conducting it was found that in the I group of patients the blood glucose level normalized: 4,4 ± 0,41 millimoles per liter, in the II group of patients this index remained in the normal range: 4,8 ± 0,4 millimoles per liter (tab. 2).

The results of OGTT showed that the use of metformin in complex therapy of patients with severe dermatoses in long-term GCs taking leads to normalization of glucose level in blood and prevents the formation of disturbances of its level in serum.

CONCLUSIONS

1. Metformin is an effective medication that prevents and treats the impaired glucose tolerance in patients with severe dermatoses on long-term therapy with glucocorticosteroid hormons.
2. The used method of examination (oral glucosetolerant test) is accessible in cost and its conducting and can be widely used for

disturbance of carbohydrate metabolism diagnostics and its therapy control in everyday practice of dermatologists.

3. Prescription of metformin during long-term therapy with glucocorticosteroids makes the use of them less dangerous for the patients, preventing the development of of long-term treatment with these drugs, what in its turn improves the quality of dermatoses therapy and sometimes allows to preserve the patients' life (for example, in true pemphigus).

Table 2

Dynamics of the blood glucose level in patients with severe dermatoses during long-term therapy with glucocorticosteroids, (M ± sd)

Glucose of capillary blood, (millimoles per liter)	I group, n=31		II group, n=41		Group of control, n=30	
	On an empty stomach	120 minutes after glucose solution taking (75g)	On an empty stomach	120 minutes after glucose solution taking (75g)	On an empty stomach	120 minutes after glucose solution taking (75g)
before metformin prescription	4,4 ± 0,6	7,9 ± 0,1†	4,8 ± 0,3†	4,7 ± 0,5	4,0 ± 0,33†	4,9 ± 0,41
after metformin prescription	4,3 ± 0,6	4,4 ± 0,4*	5,0 ± 0,1*	4,8 ± 0,4	5,0 ± 0,28*	4,2 ± 0,5

Note: * – differences are reliable ($p < 0,05$) in comparison with the index before metformin prescription;
† - differences are reliable ($p < 0,05$) in comparison with the index after metformin prescription.

PROSPECTS FOR FUTURE STUDIES

The further deeper study of glucocorticosteroids influence on the human organism and possibilities of their side effects prevention will allow to use wider these very strong and still essential medications more effectively not only in the practice of dermatologist but in another glucocorticoids-depending diseases.

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POLYOXIDONIUM EFFECT ON IMMUNOREACTIVITY OF PATIENTS WITH CHRONIC STAPHYLOCOCCOSIS PHARYNGITIS

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In this paper we have studied the effectiveness of Polioksidony in the treatment of patients with chronic staphylococcus's pharyngitis on background. It was found that the inclusion in the complex treatment of patients Polioksidony normalizes biotsinoz oropharyngeal secretions, increases the phagocytic activity of neutrophils and biocide , opsonizing properties serum normalizes the major classes of immunoglobulins in oropharyngeal secretions . Polioksidony has a positive effect on the clinical course of chronic pharyngitis and warns its recurrence, reduces the number of acute respiratory diseases and their complications.

KEY WORDS: polioksidony, chronic pharyngitis, antimicrobial immunity

ВПЛИВ ПОЛІОКСІДОНІЮ НА ІМУНОРЕКТИВНІСТЬ ХВОРИХ НА ХРОНІЧНИЙ СТАФІЛОКОККОВИЙ ФАРИНГІТ

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В роботі вивчалась ефективність застосування Поліоксідонію у комплексній терапії хворих на хронічний стафілококовий фарингіт. Встановлено, що включення в комплексне лікування хворих Поліоксідонію дозволяє нормалізувати біоценоз ротоглоткового секрету, підвищити фагоцитарну та біоцидну активність нейтрофілів, властивості сироватки, що опсонуються, нормалізувати вміст основних класів імуноглобулінів в ротоглотковому секреті. Поліоксідоній зумовлює позитивний вплив на клінічний плин хронічного фарингіту та попереджує його рецидування, зменшує кількість гострих респіраторних захворювань та їх ускладнень.

КЛЮЧОВІ СЛОВА: поліоксідоній, хронічний фарингіт, антимікробний імунітет

ВЛИЯНИЕ ПОЛИОКСИДОНИЯ НА ИММУНОРЕАКТИВНОСТЬ БОЛЬНЫХ ХРОНИЧЕСКИМ ФАРИНГИТОМ НА ФОНЕ СТАФИЛОКОККОНОСИТЕЛЬСТВА

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В работе изучена эффективность применения Полиоксидония в комплексной терапии больных хроническим фарингитом на фоне стафилококкосительства. Установлено, что включение в комплексное лечение больных Полиоксидония позволяет нормализовать биоциноз ротоглоточного секрета, повысить фагоцитарную и биоцидную активность нейтрофилов, опсонизирующие свойства сыворотки, нормализовать содержание основных классов иммуноглобулинов в сыворотке крови и ротоглоточном секрете. Полиоксидоний оказывает положительное влияние на клиническое течение хронического фарингита и предупреждает его рецидивирование, снижает количество острых респираторных заболеваний и их ослонений.

КЛЮЧЕВЫЕ СЛОВА: полиоксидоний, хронический фарингит, антимикробный иммунитет

INTRODUCTION

Long-term inflammatory processes occurring in the airway mucosa lead to inhibition of local defense mechanisms and reduce the overall immunoreactivity body [1, 2].

With the development of inflammation of the upper airway disorder observed in the immune system, including insufficient mucosal immunity. Thus, the greatest interest in the treatment of these patients and immuno-rehabilitation are immunomodulatory drugs or immunostimulatory activities [3, 4, 5].

Among immune preparations is difficult to identify drugs with distinct only immunocorrective or just immunostimulatory properties. The observed effect (or immunostimulatory immunocorrective) of using this group of drugs is determined by the initial status of the immune system of the patient and treatment scheme.

The effectiveness of the therapy of infectious and inflammatory diseases including increases in the range of therapeutic intervenetions drugs immunocorrective orientation. Today, a wide clinical application has Polioksidony (Petrovax Pharm, Russia), with a wide range of influence on the cells and organs of the immune system [6, 7].

In its chemical structure Polioksidony substances are similar to of natural origin. N-oxide groups are the base of the drug. They are commonly found in the human body, as through the formation of N0- oxide occurs the metabolism of nitrogenous compounds. The drug has a wide range of pharmacological effects on the body - an immunomodulatory, detoxifying, antioxidant and membranoprotektiv. Polioksidony factors are capable of activating innate immunity (monocytes/macrophages, neutrophils, NK), stimulate the production of cytokines that enhance antibody and cell mediated immunity and improve the quality of life of the patient. All these properties define it as an immune stimulant drug of first choice for all kinds of secondary immunodeficiency, complex treatment and prevention of diseases, including infectious origin, holding immunorehabilitation. It is important that the contraindications of Polioksidony were not detected [6]. Antioxidant and detoxifying membranoprotektiv properties of Polioksidony allow the use of this medication with antibiotics. There are studies proving the effectiveness of Polioksidony treatment of inflammatory diseases of the nasal cavity and paranasal sinuses, chronic inflammatory process in pharyngeal plexus [7].

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OBJECTIVE

The aim of this work was to study the effecttiveness of Polioksidony in treating patients with chronic staphylococcus's pharyngitis (ChPh), its impact on the clinical course of the disease and the body immunoreactivity parameters.

MATERIALS AND METHODS

We observed 62 patients on chronic staphylococcus's pharyngitis in age from 21 to 45 years, who were treated in the Communal health institution «Kharkiv city hospital № 6». The first group (basic group) amounted to 32 patients, together with anti-inflammatory therapy (topical Lizak 1 tablet 3 times daily for 7 days, physiotherapy for 5days, treatment of the posterior pharyngeal wall Lugol solution 3 times a day for 5 days) was obtained Polioksidony (6 mg every 24 hours to 5 injections, then two times a week, 10 injections for the course). The second group (control group) consisted of 30 patients who received similar therapy without Polioksidony.

Clinical, microbiological, immunological studies were performed before the treatment, at 7 and 30 days after the end of the therapy.

As indicators of standards the results of 30 healthy individuals were used.

Immunological studies included the determination of the phagocytic activity of neutronphils, their biocidity, opsonizing properties serum titers of antibodies to the causative infectious agents, concentrations of the major classes of immunoglobulins in saliva and serum.

Phagocytic activity of blood neutrophils was determined by thick smear [8]. As the object of phagocytosis using an inactivated strain of staphylococcus culture daily 209. Phagocytic number (PhN - number of phagocytic cells) and phagocytic index (PhI - the number of bacteria absorbed by one cell) were determined. The efficiency of phagocytosis of bacteria opsonized was studied in a similar manner. The opsonization of bacteria were performed in Hanks solution containing 20 % of sera from patients with thermally activated (autoserum) or serum from healthy donors (pool of 5 donors) for 30 min at 37ºC.

Biocidal phagocytes were estimated by using the S. Nielsen method [9]. The number of absorbed, but live bacteria was determined after seeding cell lysate Golda Petri method dishes

with plain agar. Lysis of leukocytes was performed by adding 3 -fold amount of water.

Antibody titer (T.Ab) to opportunistic microorganisms and antigenic determinant common (CAD) bacteria were determined by ELISA [10].

Ultrasonic disintegrants were used as the bacterial antigens prepared from one-day culture of microbial cells killed by heating for 2 hours on a boiling water bath [11].

Serum levels of immunoglobulins M, A, G were determined spectrophotometrically [12].

Mathematical processing of the data was performed using Microsoft Excel 2007 and programs MedStat (Serial number MS000055) SPDE «Alpha», Donetsk, according to the recommendations of statistical processing of biomedical materials. To identify significant differences compared indicators Student's t-test was used. The differences were considered significant at a significance level of $p < 0.05$. Data was given in the text as the arithmetic mean M and the standard deviation sd.

RESULTS AND DISCUSSION

Patients before treatment complained of pain and sore throat (84 %), foreign body sensation in the throat (32 %), dry cough (40 %) and low-grade fever (52 %).

Microbiological examination of oropharynxgeal secretions ChFh patients revealed a 34 % S. pneumonia $(3,6 \pm 0,3) \times 10^5$ CFU/ml, at 24 % - S.aureus $(3,5 \pm 0,4) \times 10^6$ CFU/ml. Microbial associations were sown in 45 % of cases, which consisted of S. pneumonia, S.aureus and Candida Albicans.

Immunological studies have shown that patients with chronic staphylococcus's pharyngitis of increasing concentrations of IgG and mIgA and reducing values sIgA and lysozyme in oropharyngeal secretions (tab. 1).

It has also been found that digesting and absorbing capability bacterial particles neutrophils peripheral blood of patients with ChPh lower than that of healthy individuals (tab. 2). Low phagocytic ability of cells to patients with HF was observed in respect of opsonized autoserum bacteria (tab. 3).

In all patients of the main group and the comparison group revealed a significant increase in antibody titer to bacterial etiological factors and common antigenic determinative (CAD) bacteria. High antibody titers were detected for almost all microbes studied (tab. 4).

The clinical observations have shown that under the influence of Polioksidony patients with chronic staphylococcus's pharyngitis, on the 7th day after the treatment has been a marked decrease or complete disappearance of the major clinical symptoms: sore throat (25 %), foreign body sensation in the throat (at 13,8 %). all patients receiving Polioksidony markedly improved overall health (normalization of body temperature in 70 %, fatigue 18 %).

Table 1

Content of lysozyme, sIgA, mIgA, IgG in the oropharyngeal secretions of patients 1 and 2 groups before and after the treatment, (M ± sd)

Indicators	Healthy persons	ChFh Patients		
		Before treatment	After treatment	
			7 days	1 month
sIgA g/l	0,30±0,03	0,22 ± 0,02* 0,21 ± 0,02*	0,26 ± 0,02* 0,22 ± 0,02*	0,28 ± 0,02†‡ 0,23 ± 0,02*
IgA g/l	0,15±0,02	0,23 ± 0,02* 0,23 ± 0,02*	0,19 ± 0,02* 0,21 ± 0,02*	0,16 ± 0,02†‡ 0,21 ± 0,02*
IgG g/l	0,063±0,03	0,076 ± 0,08* 0,075 ± 0,08*	0,068 ± 0,007* 0,071 ± 0,007*	0,064 ± 0,008†‡ 0,071 ± 0,008*
Lysozyme mg/l	458,6±25,9	338,3 ± 30,6* 337,8 ± 30,5*	452,5 ± 30,2†‡ 351,2 ± 30,4*	460,4 ± 30,6†‡ 395,1 ± 30,4*

Note: Above the line - parameters of patients of group 1, under the dash - 2 groups
* $p < 0.05$ - significant differences parameters of patients from healthy individuals,
† $p < 0.05$ - significant differences parameters of patients after treatment on the performance of patients before treatment,
‡ $p < 0.05$ - significance of differences between the indices of patients 1 and 2 groups.

Table 2

Phagocytic and biocidal activity of blood neutrophils of patients 1 and 2 groups before and after the treatment, (M ± sd)

Indicators	Healthy persons	ChFh Patients		
		Before treatment	After treatment	
			7 days	1 month
Phagocytic number (PhN),%	75,7 ± 7,1	55,6 ± 6,3* 55,4 ± 6,3*	70,2 ± 6,4†‡ 55,5 ± 6,3*	74,8 ± 6,8†‡ 57,1 ± 6,1*
Phagocytic index (PhI)	5,6 ± 0,5	3,1 ± 0,4* 3,1 ± 0,4*	4,7 ± 0,4†‡ 3,2 ± 0,4*	5,3 ± 0,6†‡ 3,7 ± 0,4*
Bactericidal activity,%	4,8 ± 0,6	17,7 ± 1,6* 17,8 ± 1,6*	6,4 ± 0,6*†‡ 17,2 ± 1,8*	5,4 ± 0,6†‡ 15,2 ± 1,4*†

Note: Above the line - parameters of patients of group 1, under the dash - 2 groups
* p < 0.05 - significant differences parameters of patients from healthy individuals,
† p < 0.05 - significant differences parameters of patients after treatment on the performance of patients before treatment,
‡ p < 0.05 - significance of differences between the indices of patients 1 and 2 groups.

Table 3

Phagocytic activity of neutrophils of patients 1 and 2 groups regarding autoserum opsonized bacteria before and after the treatment, (M ± sd)

Indicators	Healthy persons	ChFh Patients		
		Before treatment	After treatment	
			7 days	1 month
Phagocytic number (PhN),%	81,0 ± 7,1	58,4 ± 6,6* 58,5 ± 6,6*	78,2 ± 6,4†‡ 58,7 ± 6,5*	80,2 ± 7,6†‡ 63,7 ± 6,1*
Phagocytic index (PhI)	5,8 ± 0,5	3,1 ± 0,3* 3,1 ± 0,3*	4,7 ± 0,4†‡ 3,2 ± 0,3*	5,9 ± 0,6†‡ 4,1 ± 0,4*
Bactericidal activity,%	3,1 ± 0,4	17,3 ± 1,8* 17,2 ± 1,8*	4,9 ± 0,5†‡ 17,0 ± 1,6*	3,7 ± 0,4†‡ 11,9 ± 1,3*†

Note: Above the line - parameters of patients of group 1, under the dash - 2 groups
* p <0.05 - significant differences parameters of patients from healthy individuals,
† p <0.05 - significant differences parameters of patients after treatment on the performance of patients before treatment,
‡ p <0.05 - significance of differences between the indices of patients 1 and 2 groups.

Table 4

The Antibody titer (relative unit) to infectious agents in patients 1 and 2 groups before and after the treatment, (M ± sd)

Microbes	ChFh Patients		
	Before treatment	After treatment	
		7 days	1 month
S. pneumoniae	1,5 ± 0,1* 1,5 ± 0,1*	1,8 ± 0,1*† 1,7 ± 0,1*	2,0 ± 0,2*†‡ 1,7 ± 0,1*
S. aureus	1,4 ± 0,1* 1,4 ± 0,1*	1,7 ± 0,1*† 1,6 ± 0,1*	1,8 ± 0,1*†‡ 1,6 ± 0,1*
C bacteria	1,5 ± 0,1* 1,5 ± 0,1*	1,8 ± 0,1*† 1,6 ± 0,1*	1,9 ± 0,1*†‡ 1,6 ± 0,1*

Note: Above the line - parameters of patients of group 1, under the dash - 2 groups
* p < 0,05 - significant differences parameters of patients from healthy individuals,
† p < 0,05 - significant differences parameters of patients after treatment on the performance of patients before treatment,
‡ p < 0,05 - significance of differences between the indices of patients 1 and 2 groups.

When instrumental examination of all patients of the main group and the comparison group on the 7th day after the end of treatment was observed swelling and hypertrophy of the mucous membrane of the posterior pharyngeal wall.

On the 30th day after the end of treatment, 71.8 % of the study group patients without complaints (in the comparison group - 30 % of patients), and their clinical status was characterized by the norm. Pharyngoscope at 84,3 % of the patients of the main group and in all patients of the comparison group experienced a slight hypertrophy of the mucous membrane of the posterior pharyngeal wall.

Microbiological examination of the main group found in 84,3 % of cases the absence of pathogens (from 9,3 % - S. pneumonia (3,1 ± 0,3) × 10^3 CFU/ml, at 6,4 % - S.aureus (2,3 ± 0,3) × 10^3 CFU/ml), marked decrease in microbial associations (in 15,6 % of patients) without the appearance of fungal flora and 68 % of the pathogenic microflora (S. epidermi-dis (2,1 ± 0,3) × 10^3 CFU/ml, S. saprophyticus (3,3 ± 0,2) × 10^2 CFU/ml).

In the control group half of the patients (52 %) was sown pathogenic flora (S. pneumonia (3,1 ± 0,3) × 10^4 CFU /ml, S.aureus (2,3 ± 0,3) × 10^5 CFU/ml) a slight decrease in the amount of microbial associations (36.6 % cases).

Immunological studies have shown that under the influence of the dynamic changes occurring Polioksidony and immunoreactivity in patients. However, they are somewhat delayed in time as compared with the clinical improvement.

Under the effect of Polioksidony the increase of the secretory IgA and serum immunoglobulins (IgA and IgG), and lysozyme occurred in the content of oropharyngeal secretions (tab. 1).

On the 7th day after the treatment the patients receiving Polioksidony, had a significant increase in the phagocytic activity of neutrophils and biocide effect, and increase serum opsonizing properties (tab. 2, 3).

The autoserum increased both in the absorption capacity of neutrophils and their biocidal effect. Full restoration of the functional activity of phagocytic cells in these patients occurred by 30 days after treatment. To compare the group of patients we have studied that the properties of cells and serum opsonizing properties recovering very slowly and by 30 days were significantly different from the norm.

On the 7th and 30th days after the end of the treatment the patients who received Polioksidony, had an increase in antibody titer to infectious etiologic pathogens and IgG antibodies to CAD bacteria (tab. 4).

It appears that the long circulation in patients with high titers of antimicrobial antibodies with high affinity is an important factor in the suppression and elimination of infectious agents, as well as a factor preventing the recurrence of the disease. The patients who did not receive Polioksidony such dynamic improvements in humoral immunity were observed. By 30th days after the treatment the patients in a comparison group the antibody titer to infectious etiologic pathogens and their affinity were not significantly changed compared to their values before treatment (tab. 4).

The monitoring of patients during the year showed that the main group was not observed recurrence ChFh. They are much less likely than the comparison group was ill patients with acute respiratory infections, which are mild and not accompanied by complications. In the study group acute respiratory infections 2-4 times a year have been reported in 17 % of patients.

Patients with ChFh comparison group relapses occurred in 40 % of cases, of which 25 % of patients - 2-3 times a year, 70 % of patients 2-4 times a year suffered acute respiratory illness, which in 23,8 % of cases complicated by acute bronchitis. In 3 patients (10 %) were diagnosed with pneumonia.

CONCLUSIONS

1. Polioksidony has a positive effect both on the clinical course of chronic pharyngitis and prevention of its recurrence, and the immunoreactivity of the body.

2. Polioksidony stimulates the increase of phagocytic and biocidal activity of white blood cells, the production of high affinity antibodies antimicrobial, increased serum opsonin properties.

The findings showed promising applications and high therapeutic efficacy of Polioksidony in the treatment of chronic staphylococcus's pharyngitis.

PROSPECTS FOR FUTURE STUDIES

Prospects for future studies is a comparative analysis of the treatment of chronic and acute pharyngitis by immunomodulatory drugs.

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IMMUNOREACTIVITY OF CHILDREN OF DIFFERENT AGES WITH THE CEREBRO-ASTHENIC SYNDROME, WHO WERE PREMATURELY BORN WITH PERINATAL DEFEAT OF CENTRAL NERVOUS SYSTEM

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The immune status and nature of immune frustration of children of different ages with the cerebral asthenic syndrome (CAS), who were prematurely born with perinatal defeat of the central nervous system (CNS) was studied. The obtained data argue that these children have the expressed imbalance among Th-cages (Th1, Th2, Treg) and cytokines that shows the potential risk of inadequate reaction of these children on infectious and noninfectious immunogenes.

KEY WORDS: cerebro-asthenic syndrome, perinatal defeat of central nervous system, prematurely born children, immunoglobulins, cytokines

ИММУНОРЕАКТИВНІСТЬ ДІТЕЙ РІЗНОГО ВІКУ З ЦЕРЕБРАСТЕНІЧНИМ СИНДРОМОМ, ЩО НАРОДИЛИСЯ НЕДОНОШЕНИМИ З ПЕРИНАТАЛЬНИМ УРАЖЕННЯМ ЦЕНТРАЛЬНОЇ НЕРВОВОЇ СИСТЕМИ

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Вивчено імунний статус і характер імунних розладів у дітей різного віку з церебрастеничним синдромом (ЦАС), що народилися недоношеними з перинатальним ураженням центральної нервової системи (ЦНС). Отримані дані свідчать про те, що ці діти мають виражений дисбаланс серед Th-клітин (Th1, Th2, Treg) і цитокінів, що вказує на потенційний ризик неадекватного реагування цих дітей на інфекційні та неінфекційні імуногени.

КЛЮЧОВІ СЛОВА: церебрастенічний синдром, перинатальне ураження центральної нервової системи, недоношені діти, імуноглобуліни, цитокіни

ИММУНОРЕАКТИВНОСТЬ ДЕТЕЙ РАЗНОГО ВОЗРАСТА С ЦЕРЕБРАСТЕНИЧЕСКИМ СИНДРОМОМ, РОДИВШИХСЯ НЕДОНОШЕННЫМИ С ПЕРИНАТАЛЬНЫМ ПОРАЖЕНИЕМ ЦЕНТРАЛЬНОЙ НЕРВНОЙ СИСТЕМЫ

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Изучен иммунный статус и характер иммунных расстройств у детей разного возраста с церебрастеническим синдромом (ЦАС), родившихся недоношенными с перинатальным поражением центральной нервной системы (ЦНС). Полученные данные свидетельствуют о том, что эти дети имеют выраженный дисбаланс среди Th- клеток (Th1, Th2, Treg) и цитокинов, что указывает на потенциальный риск неадекватного реагирования этих детей на инфекционные и неинфекционные иммуногены.

КЛЮЧЕВЫЕ СЛОВА: церебрастенический синдром, перинатальное поражение центральной нервной системы, недоношенные дети, иммуноглобулины, цитокины

INTRODUCTION

Formation and development of immune system begins at early children's age and resistance of an organism to infectious and noninfectious diseases depends on its nature of functioning. In recent years indicators of survival of the prematurely born children with low body weight has significantly improved. However during postnatal development, prematurely born children have difficulties of medical and social adaptation, a delay of physical and psycho-emotional development could be attended with high incidence.

According to A.A. Baranov, in recent years pathology of nervous system in the perinatal period has increased almost in two times [1]. The injury of a brain, concerned with cerebral hypoxia, occurs to 60-80 % of newborns [2]. Hypoxic-ischemic encephalopathies are the reason of high mortality in the neonatal period and lead to various nervous disorders in children, defining the quality of life in future [3, 4, 5].

OBJECTIVE

According to all mentioned above and also close interrelation of nervous and immune system, the purpose of our work is the study of the immune status and nature of immune frustration in children of different ages with the cerebro-asthenic syndrome (CAS), who were prematurely born with a perinatal lesion of central nervous system.

MATERIALS AND METHODS

We have surveyed 56 children with CAS at the age of 6-7 years and 58 children at the age of 12-14 years, born prematurely with perinatal lesions of CNS (primary group). The group of comparison comprised children with CAS of the same age (44 children at the age of 6-7 years and 48 children at the age of 12-14 years), born in time without perinatal CNS disorders. The control group was made by almost healthy children of the same age (30 children - 6-7 years and 30 children - 12-14 years).

Criteria of an exception were chronic diseases of inner organs: cardiovascular system diseases, chronic infectious diseases, chronic diseases of endocrine system, serious chronic illness of nervous system (epilepsy, infantile cerebral paralysis, hydrocephaly, consequences of heavy craniocerebral traumas).

Examination of children was conducted on the basis of the Regional center of children's immunology Kharkiv Regional children's clinical hospital № 1 (№ 1 RCCH) and the Department of the general and clinical immunology and allergology of V.N. Karazin Kharkiv National University.

The diagnosis of cerebral asthenic syndrome was determined according to ICD-10, verified on the base of pathognomonic clinical manifestations of the disease and data of laboratory and instrumental examinations.

The program of immunological investigations included evaluation of lysozyme, secretory immunoglobulin A (IgA), monomeric IgA, immunoglobulin G (IgG) levels in an oral secret, the main classes of immunoglobulins (IgA, IgG, IgM) in serum of blood, immunoglobulin E (IgE), circulating immune complex (CIC), complement, population and subpopulation structure of lymphocytes in peripheral blood, the content of the main inflammatory and anti-inflammatory cytokines. The content of lysozyme in an oral secret was determined early in the morning fasting by a diffusion method in an agar [6]. The concentration of immunoglobulin of various classes in an oral secret and serum of blood was defined by spectrofluorimetry [7], concentration of immunoglobulin E - enzyme-linked immunosorbent assay (IgE-ELISA) - according to the enclosed instruction. The level of CIC in serum of blood was determined by the method of selective precipitation with polyethylene glycol (PEG) – 6000 [8]. The activity of compliment was judged on 50% hemolysis test system [8].

Population structure of lymphocytes in peripheral blood was determined by a method of a flowing laser cytometry with use of monoclonal antibodies of different specificity, on the FACSC Calibun device (USA). The maintenance of Th1 and Th2-cells was evaluated according to the content of IL-4 and IFNγ in cytoplasm of lymphocytes [9, 10].

Proliferative activity of lymphocytes was estimated at reactions of a blast-cell transformation of lymphocytes with phytohemagglutinin [11]. Intensity of reaction estimated morphologically in a percentage of formed blastic variant.

The content of cytokines in serum of blood was determined by the enzyme-linked immunoassay method according to the enclosed instruction. It was used commercial test systems

produced by «Vektor-Best» (village Koltsovo, the Novosibirsk Region, Russia).

The statistical data processing was carried out by Microsoft XL 2007 and the Med Stat program (serial № MS000055) by DIVP TOV «Alpha», Donetsk, according to the recommendations of statistical processing of biomedical data [12, 13]. It was carried out the checking of selections on a normality of distributions (criterion x2), calculated average arithmetic (M), and an average error of the average size (m), determined reliability of distinctions by criterion of Student's *t* distribution. The critical level of significance was equal to 0,05 [14, 15, 16].

RESULTS AND DISCUSSION

The study of local oral immunity showed that in children with CAS who were prematurely born with perinatal lesion of CNS and children with CAS, born in time without perinatal disorders of CNS, the content of lysozyme, s-IgA, m-IgA, IgG, authentically did not differ from the children of control group. In children of 6-7 years and children of 12-14 years all studied indicators were within physiological age norm. Also reliable distinctions were not revealed in these groups of children in the content of the main classes of immunoglobulin (IgA, IgG, IgM), IgE, CIC and the complement in serum of blood.

Study of population and subpopulation structure of lymphocytes of peripheral blood of children of 6-7 years and 12-14 years with CAS who were prematurely born with perinatal lesion of CNS, revealed a tendency of decrease in the content of T-general lymphocytes (CD3+), CD4+-cells, decrease in proliferative activity of lymphocytes in blast-transformation reaction (BTR) with phytohemagglutinin (PHA), reliable reduction in contents Treg-of cells and relative increase of the contents among subpopulation of Th-of lymphocytes of Th1-of cells (tab. 1). These children have the imbalance in the ratio of Th1\Th2-cells, Th1/Treg-cells, which was connected with increasing of a share of Th1-lymphocytes among subpopulation of Th-of cells, and also an imbalance between Th2 and Treg caused by decrease of share of Treg-cells in population of lymphocytes.

Table 1

Population and subpopulation structure of lymphocytes of peripheral blood of children of 6-7 years and 12-14 years with CAS who were prematurely born with perinatal lesion of CNS and born in time without perinatal lesion of CNS, (M ± m)

Indices	Children with perinatal lesion of CNS		Children without perinatal lesion of CNS		Control group	
	6-7 years	12-14 years	6-7 years	12-14 years	6-7 years	12-14 years
Lymphocytes, %	30,9 ± 1,80	31,2 ± 1,81	31,7 ± 1,80	31,8 ± 1,80	34,1 ± 1,83	3,21 ± 1,72
Absolute number	2,23 ± 0,13	2,11 ± 0,11	2,39 ± 0,13	2,20 ± 0,12	2,48 ± 0,12	2,23 ± 0,11
CD 3 + cl, %	57,23 ± 3,14	58,9 ± 3,41	58,1 ± 3,19	59,6 ± 3,46	62,5 ± 3,31	65,7 ± 3,42
CD4 + cl, %	35,9 ± 2,01	36,0 ± 2,01	36,3 ± 2,01	36,9 ± 2,00	39,7 ± 2,02	39,1 ± 2,01
CD8 + cl, %	21,1 ± 1,21	22,6 ± 1,32	22,0 ± 1,24	22,4 ± 1,24	22,3 ± 1,15	24,9 ± 1,22
CD19 + cl, %	23,0 ± 1,18	21,9 ± 1,07	23,6 ± 1,18	23,1 ± 1,18	23,6 ± 1,17	22,3 ± 1,09
CD16 + cl, %	11,4 ± 1,12	11,9 ± 1,12	11,3 ± 1,12	11,6 ± 1,12	11,3 ± 1,03	12,0 ± 1,19
BTR with PHA, %	42,0 ± 7,32	45,8 ± 7,44	45,1 ± 7,31	46,7 ± 7,45	56,7 ± 7,93	59,7 ± 9,04
BTR, %	9,3 ± 0,87	9,4 ± 0,88	9,0 ± 0,88	9,0 ± 0,89	7,9 ± 0,61	8,1 ± 0,82
Th1- cl ,%	6,7 ± 0,69*†	7,3 ± 0,78*†	5,2 ± 0,58*	5,6 ± 0,62*	4,0 ± 0,43	4,3 ± 0,49
Th2- cl, %	4,3 ± 0,57	4,8 ± 0,53	46,0 ± 0,52	4,9 ± 0,54	4,9 ± 0,51	5,2 ± 0,54
Treg, %	7,1 ± 0,73*	7,3 ± 0,73*	8,6 ± 0,89	8,9 ± 0,91	10,2 ± 1,00	10,9 ± 1,04
Th1/Th2	1,55 ± 0,16*†	1,51 ± 0,16*†	1,13 ± 0,12*	1,14 ± 0,12*	0,81 ± 0,08	0,82 ± 0,08
Th1/Treg	0,94 ± 0,98*†	1,00 ± 0,06*†	0,60 ± 0,06*	0,62 ± 0,06*	0,39 ± 0,04	0,39 ± 0,04
Th2//Treg	0,60 ± 0,06*	0,65 ± 0,06*	0,53 ± 0,06	0,55 ± 0,06	0,48 ± 0,05	0,47 ± 0,05

Note: * $p < 0,05$ - between indicators of children with CAS and children of control group,

† $p < 0,05$ - between indicators of children who were been prematurely born with perinatal lesion of CNS and children who were born in time without perinatal lesion of CNS.

Children of 6-7 years and 12-14 years with CAS born in time without perinatal defeat of CNS, similar changes in population and subpopulation structure of lymphocytes of peripheral blood were observed (tab. 1). However, in comparison of children born with perinatal defeat of CNS, with children without perinatal defeat of CNS it was not observed reliable decreasing in quantity Treg-cells in blood and an imbalance in the content of Th2-cells and Treg-cells, in comparison with norm. Increasing of the share of Th1-cells in peripheral blood, and also imbalance of Th1/Th2 and Th1/Treg, children prematurely born with perinatal lesion of CNS was much higher, than in time born children without perinatal defeat of CNS and statistically reliable ($p < 0,05$).

The obtained data testifies that the children with CAS in the main and comparison group have frustrations in T-cellular of immunity which are considerably related to an imbalance among subpopulations of the Th-cells which are possessing regulatory potential. Degree of frustration of children of 6-7 years and 12-14 years who were prematurely born with perinatal lesion of CNS is much higher, than of the children of the same age, who were born in time without perinatal lesion of CNS (tab. 1).

For the assessment of the cytokine status of children with CAS there have been chosen cytokines with regulatory properties: IL-1β, IL-2, IL-4, IL-6, INFγ, IL-10, TNFα.

IL-1 – plays an important role in development of reactions of adaptive immunity, assists to activation and maturation of B - cells, an expression on T – cells of receptor to IL-2, formation of molecules of the major histocompatibility complex (MHS), pertains to the category of pro-inflammatory cytokines.

IL-2 – plays the central role in development T-cellular immunity, it is a factor of the growth and differentiation of T-lymphocytes, stimulates differentiation of Th1 and cytolytic T lymphocyte (CTL), activates the lytic activity of a NK-cells.

IL-4 and IL-6 take part in development of the antibody response, stimulate proliferation and differentiation of B-lymphocytes into antibody producers. IL-4 activates production of IgE and development of allergic reactions, induces formation of Th2 cells, suppresses development of Th1 cells and Th17 cells.

IL-6 – has the pro-inflammatory properties.

INFγ – stimulates differentiation of Th0 in Th1–cell, suppresses development of Th2 cells, activates macrophages of the NK-cells, stimulates IgG2 development, suppresses production of IgG1, IgG3, IgE.

IL-10 suppresses the function of Th1–cells, production of INFγ, IL-2, synthesis of pro-inflammatory cytokines – IL-1, IL-6, FNOα, it is a co-stimulant of reproduction and developing of B-cells, it belongs to the family of anti-inflammatory cytokines.

TNFα has antineoplastic and antiviral action, stimulates microbicidal activity of neutronnphils, macrophages, and has prion-flammatory properties.

The investigations which were made showed us that the children of 6-7 years and 12-14 years with CAS who were prematurely born with perinatal lesion of CNS, had the increase respectively in 2,4 and in 2,1 times of the contents of IL-1β, decrease of the content in 1,46 and 1,35 times of IL-2 and in 1,20 and 1,19 times of IL-10 in peripheral blood (tab. 2). The children of this group had the imbalance in the ratio IL-1/IL-10 (children of 6-7 years - $0,64 \pm 0,06$ and children of 12-14 years $0,59 \pm 0,60$, in control group respectively $0,22 \pm 0,02$ and $0,24 \pm 0,02$), IL-2/IL-4 (respectively $0,11 \pm 0,01$ and $0,12 \pm 0,01$, in control $0,18 \pm 0,01$), IL-2/IL-6 ($0,10 \pm 0,01$ and $0,11 \pm 0,01$ in control $0,15 \pm 0,01$ and $0,16 \pm 0,01$) ($p < 0,05$).

In children of 6-7 years and 12-14 years with CAS who were born in time without perinatal lesion of CNS, it was noted only reliable increasing of concentration IL-1β, in comparison with children of control group. They, as well as the children of a primary group, had the imbalance in the ratio IL-1/IL-10 (children of 6-7 years $0,42 \pm 0,04$, children of 12-14 years $0,39 \pm 0,04$, in control respectively $0,22 \pm 0,02$ and $0,24 \pm 0,02$). The ratio of IL-2/IL-10 and IL-2/IL-6 was normal. It is necessary to notice that content of IL-1β of peripheral blood of children with CAS, without perinatal lesion of CNS was lower, than in children with CAS, with perinatal lesion of CNS, IL-10-is slightly higher, and the content of IL-2 of children who were born in time without perinatal lesion of CNS, as opposed to children who were been prematurely born with perinatal lesion of CNS, authentically did not differ from values of norm.

Table 2

Contents of cytokines in serum of blood in children of 6-7 years and 12-14 years with CAS who were prematurely born with perinatal lesion of CNS and born in time without perinatal lesion of CNS, (M ± m)

Indicators	Children with perinatal lesion of CNS		Children without perinatal lesion of CNS		Control group	
	6-7 years	12-14 years	6-7 years	6-7 years	12-14 years	6-7 years
IL-1 β pg/ml	4,3 ± 0,41*†	3,9 ± 0,38*†	3,3 ± 0,35*	2,9 ± 0,30*	1,8 ± 0,20	1,9 ± 0,20
IL-2 pg/ml	1,3 ± 0,11*†	1,4 ± 0,11*†	1,6 ± 0,14	1,7 ± 0,14	1,9 ± 0,20	1,9 ± 0,20
IL-4 pg/ml	11,4 ± 1,10	11,1 ± 1,11	11,0 ± 1,10	10,7 ± 1,10	10,3 ± 1,12	10,1 ± 1,10
IL-6 pg/ml	12,5 ± 1,18	12,0 ± 1,18	12,2 ± 1,15	11,9 ± 1,17	12,1 ± 1,13	11,5 ± 1,14
IL-10 pg/ml	6,7 ± 0,70	6,6 ± 0,70	7,7 ± 0,81	7,4 ± 0,76	8,1 ± 0,80	7,9 ± 0,80
TNF pg/ml	0,7 ± 0,08	0,6 ± 0,07	0,7 ± 0,08	0,6 ± 0,07	0,7 ± 0,07	0,6 ± 0,6
INF γ pg/ml	9,8 ± 0,91	9,7 ± 0,92	9,7 ± 0,92	9,6 ± 0,93	9,9 ± 0,97	9,8 ± 0,96

Note: * $p < 0,05$ - between indicators of children with CAS and children of control group.
† $p < 0,05$ - between indicators of children who were been prematurely born with perinatal lesion of CNS and children who were born in time without perinatal lesion of CNS.

The obtained data testify that children with CAS who were prematurely born with perinatal disorders of CNS had the expressed imbalance in the contents of the main regulatory of cytokines. Revealed imbalance among Th-cells (Th1, Th2, Treg) and cytokines, of children with CAS who were prematurely born with perinatal lesion of CNS, which regulate an orientation and full value of development of immune reaction indicates to the potential risk of inadequate reaction of these children on infectious and noninfectious immunogenic that can lead to development of an immunodeficient status and synchronization of an infection or, per contra, to hyper reactions, an autosensibilization and developing of autoimmune processes. The obtained data testify that this category of children needs special attention and dispensary registration.

CONCLUSIONS

Children with CAS who were prematurely born with perinatal lesion of CNS, the frustrations in immune system concern T–cell part of immunity and are mainly connected with an imbalance of subpopulations in Th–cell (Th1, Th2, Treg) and in the cytokine network, the increased content of IL-1β and the decreased content of IL-10 and IL-2, which are responsible for the development of immune reaction. The obtained data indicates the risk of inadequate reaction on infectious and noninfectious immunogenes in these children that can lead to the development of an immunodeficiency state and chronization of an infection or, on the contrary, to hyper reactions, autosensibilization and development of autoimmune processes.

PROSPECTS FOR FUTURE STUDIES

Further it is obviously very important the selection of the immunocorrecting preparation for studying of efficiency of correction of the revealed violations.

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FREQUENCY OF DETACHED CARDIAC DRUGS PRESCRIBING IN PATIENTS OF DIFFERENT CLASSES QRS COMPLEX DURATION ON THE PERMANENT PACING BACKGROUND

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The frequency of beta-blockers, amiodarone, antiplatelet agents (acetylsalicylic acid), anticoagulants (warfarin), statins, angiotensin-converting enzyme inhibitors, diuretics and angiotensin II receptor antagonists prescribing was determined in 114 patients (56 – women, 58 – men) with permanent pacemakers in VVI/VVIR (40 patients), DDD/DDDR (26 patient), cardiac resynchronization therapy (14 patients) and separate group was made up of 34 patients with sinus sick syndrome in DDD/DDDR pacing mode in 3 QRS complex duration classes: 1 – under 119 ms (normal), 2 – 120-149 ms (elongate) and more than 150 ms (significantly elongate). The patients' average age was 69 ± 7 years. The results showed that the same groups of drugs are being prescribed as in patients with pacemakers as in patients without them. More frequent prescribing of beta-blockers was associated with prevention of the development of possible device-induced arrhythmias and chronic heart failure. More rare appointment acetylsalicylic acid and statins was associated with the lack of attention to therapeutic support. Frequency of prescribing most of used drugs in patients with implanted pacemaker increases with QRS complex duration class.

KEY WORDS: permanent pacing, QRS complex duration, cardiac drugs

ЧАСТОТА ПРИЗНАЧЕННЯ ОКРЕМИХ ГРУП КАРДІОЛОГІЧНИХ ПРЕПАРАТІВ У ПАЦІЄНТІВ У РІЗНИХ КЛАСАХ ТРИВАЛОСТІ QRS КОМПЛЕКСУ ПРИ ПОСТІЙНІЙ ЕЛЕКТРОКАРДІОСТИМУЛЯЦІЇ

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Вивчена частота призначення бета-блокаторів, аміодарону, антиагрегантів (ацетилсаліцилової кислоти), антикоагулянтів (варфарину), статинів, інгібіторів ангіотензин-перетворюючого ферменту, антагоністів рецепторів ангиотензіну II і діуретиків у 114 пацієнтів (56 – жінок, 58 – чоловіків) віком 69 ± 7 років з імплантованими електрокардістимуляторами в режимах стимуляції VVI/VVIR (40 пацієнтів), DDD/DDDR (26 пацієнт) і окремо з синдромом слабкості синусового вузла (34 пацієнт), кардиоресинхронізуючою терапією (14 пацієнтів) в 3 виділених класах тривалості QRS комплексу: 1 – до 119 мс (нормальний), 2 – 120-149 мс (подовжений) і 3 – більше 150 мс (значно подовжений). У пацієнтів з імплантованими електрокардіостимуляторами у терапевтичному супроводі використовуються ті ж групи лікарських препаратів, що і у пацієнтів поза електрокардіостимуляції. Більш часте призначення бета-блокаторів у них пов'язано з необхідністю профілактики розвитку можливих ЕКС-індукованих аритмій, і більш рідкісне призначення ацетилсаліцілової кислоти і статинів – у зв'язку з недостатньою увагою до їх терапевтичному супроводу. Частота призначення більшості використовуваних лікарських препаратів у пацієнтів з імплантованими електро-кардістимуляторами наростає із збільшенням класу тривалості QRS комплексу.

КЛЮЧОВІ СЛОВА: постійна електрокардіостимуляція, тривалість QRS комплексу, кардіологічні препарати

ЧАСТОТА НАЗНАЧЕНИЯ ОТДЕЛЬНЫХ ГРУПП КАРДИОЛОГИЧЕСКИХ ПРЕПАРАТОВ У ПАЦИЕНТОВ В РАЗНЫХ КЛАССАХ ПРОДОЛЖИТЕЛЬНОСТИ QRS КОМПЛЕКСА ПРИ ПОСТОЯННОЙ ЭЛЕКТРОДИОСТИМУЛЯЦИИ

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Изучена частота назначения бета-блокаторов, амиодарона, антиагрегантов (ацетилсалициловой кислоты), антикоагулянтов (варфарина), статинов, ингибиторов ангиотензин превращающего фермента, антагонистов рецепторов ангиотензина II и диуретиков у 114 пациентов (56 – женщин, 58 – мужчин) в возрасте 69 ± 7 лет с имплантированными электрокардиостимуляторами в режимах стимуляции VVI/VVIR (40 пациентов), DDD/DDDR (26 пациент) с АВ-блокадой и отдельно с синдромом слабости синусового узла (34 пациент), кардиоресинхронизирующей терапией (14 пациентов) в 3 выделенных классах продолжительности QRS комплекса: 1 – до 119 мс (нормальный), 2 – 120-149 мс (удлиненный) и более 150 мс (значительно удлиненный). Результаты показали, что у пациентов с имплантированными ЭКС в терапевтическом сопровождении используются те же группы лекарственных препаратов, что и у пациентов вне ЭКС. Более частое назначение бета-блокаторов у них связано с необходимостью профилактики развития возможных ЭКС-индуцированных аритмий и хронической сердечной недостаточностью, и более редкое ацетилсалициловой кислоты и статинов – в связи с недостаточным вниманием к их терапевтическому сопровождению. Частота назначения большинства используемых лекарственных препаратов нарастает с увеличением класса продолжительности QRS комплекса.

КЛЮЧЕВЫЕ СЛОВА: постоянная электрокардиостимуляция, продолжительность QRS комплекса, кардиологические препараты

INTRODUCTION

QRS complex as electrocardiograph phenomenon is a measure of the duration of one of the most critical periods of systole, namely isovolumetric contraction [1]. The increase of QRS complex duration is considered as independent predictor of increased mortality and rehospitalization in patients with chronic heart failure (CHF) with reduced ejection fraction (EF) and coronary heart disease (CHD) [2-4], including with implanted pacemakers [5].

The drugs which are used in patients with pacemaker affect not only the work of the device, but QRS complex duration also. That is why the influence of these drugs cannot be ignored [6]. Studies which investigate drugs effects on different QRS complex duration are limited [7-9], concerning patients with pacemaker are united [10], and taking into account QRS complex duration were not conducted.

OBJECTIVE

The purpose of this study is to evaluate the frequency of prescribing different groups of cardiac drugs in patients with permanent pacemaker in QRS complex duration classes.

MATERIALS AND METHODS

114 patients (56 – women, 58 – men) who underwent permanent pacemaker therapy were examined in the department of ultrasound, clinical and instrumental diagnosis and minimally invasive technologies SI «Zaitsev V.T. Institute of General and Emergency Surgery NAMS of Ukraine» in pacing modes VVI/VVIR (40 patients), DDD/DDDR (26 patients) with atrio-ventricular block (AV-block) and separately with sick sinus syndrome (SSS) (34 patients), cardiac resynchronization therapy (CRT) (14 patients) in 3 selected QRS complex duration classes: 1 – under 119 ms (normal) , 2 − 120-149 ms (extended) and more than 150 ms (significantly extended). Patients' average age was 69 ± 7 years.

QRS complex duration was measured as the average of three consecutive ECG complexes in leads II, V5, V6 on the computer electrocardiograph Cardiolab+2000 in the early postoperative period (third - fifth day after pacemaker implantation).

Frequency of beta-blockers, amiodarone, antiplatelet agents (acetylsalicylic acid), anticoagulants (warfarin), statins, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor antagonists II (ARA II) and diuretics was determined.

Frequency of different groups cardiac drugs prescribing was calculated in the relative units (p, %) in Microsoft Excel, and the average error percentage (sp) was determined too. The significance of differences between the values in QRS complex duration classes was estimated using the non-parametric U-Mann−Whitney test. The differences were considered as reliable if $p < 0.05$.

RESULTS AND DISCUSSION

Frequency of different groups of cardiac drugs prescribing in patients with implanted pacemaker is presented in table.

Table

Frequency of different groups of cardiac drugs prescribing in QRS complex duration classes, (% ± sp)

Drugs	Total patients, n	Frequency of prescribing			
		Total	QRS complex duration classes, (ms)		
			< 119	120-149	> 150
Beta-blockers	68	60 ± 5	30 ± 15	41 ± 6**	86 ± 5***
Amiodarone	17	15 ± 3	10 ± 9	13 ± 5	18 ± 5
Antiplatelet agents (acetylsalicylic acid)	34	30 ± 4	30 ± 15	22 ± 6	38 ± 7
Anticoagulants (warfarin)	12	11 ± 3	10 ± 9	9 ± 4	12 ± 5
Statins	29	25 ± 4	20 ± 13	19 ± 5**	34 ± 7
ACE inhibitors	70	61 ± 5	40 ± 15	43 ± 7**	94 ± 3***
ARA II	32	28 ± 4	10 ± 9	17 ± 5	24 ± 6
Diuretics	26	23 ± 4	20 ± 13	17 ± 5	30 ± 6

Legend: n − the absolute value; sp − average error rate;
* p <0.05 − reliable level of differences in QRS complex duration classes 1 and 2;
** p <0.05 − reliable level of differences in QRS complex duration classes 2 and 3;
*** p <0.05 − reliable level of differences in QRS complex duration classes 1 and 3.

Beta-blockers and ACE inhibitors were prescribed more frequently in the studied groups of drugs. The frequency of their prescribing was the same, what corresponds to the data [11, 12]. The frequency of their prescribing was increased from one to another QRS complex duration classes, as well as increased functional classes of CHF in patients with extended and significantly extended QRS complex. The frequency of beta -blockers prescribing in patients with implanted pacemaker was higher than in patients without pacemaker, what was associated with the possible development of pacemaker-induced arrhythmias [13].

The next most frequently prescribed drugs were antiplatelet agents (ASA) and ARA II, it was identified no significant differences in their prescription between QRS complex duration classes. We did not found the literature data on the frequency of ASA and ARA II prescription in patients with implanted pacemaker. The frequency of ASA prescription in our group of patients was significantly lower than in patients without implanted pacemaker [14], and the frequency of ARA II prescription corresponded to that in patients without pacemaker [15].

Despite the fact that statins are shown a greater extent in patients with permanent pacemaker vs. patients without pacemaker, due to their pleiotropic anti-fibrotic and antiarrhythmic effects regarding the possible development of atrial fibrillation (AF) [16, 17], they were prescribed only in 25 % of our patients, what was significantly lower frequency than in patients with coronary atherosclerosis without pacemaker, which was more than 53 % according to a study EUROASPIRE II [18]. Increased frequency of statin use in class 3 against classes 1 and 2

QRS complex duration was explained by more severe condition of this class of patients.

Diuretics and amiodarone were more rarely prescribed, and it was identified no significant differences in the frequency of prescribing between QRS complex duration classes. It is known that diuretics prescribing and as a result hypokalemia is associated with QRS complex duration prolongation [19].

Warfarin was the least administered drug. It was prescribed in patients with atrial fibrillation mainly. Strategy of continuous warfarin therapy is associated with reduced risk of thromboembolic complications in these patients with a background on permanent pacing [20].

The frequency of calcium channel blockers, ivabradine, digoxin, direct peroral anticoagulants did not taken into account in our study because of their infrequent use.

In accordance with the results obtained in patients with permanent pacemaker the same groups of cardiac drugs are used as in patient without pacing, however, the frequency of assignment between the drugs can be substantially different. Significantly more frequent use of beta-blockers in patients with permanent pacemaker was explained by arrhythmogenic effects of pacing therapy [13]. Less frequent use of drugs of other groups may be exists due to insufficient attention to their therapeutic support. The frequency of cardiac drug prescribing in patients with permanent pacemaker is significantly affected by the QRS complex duration class.

CONCLUSIONS

1. The same groups of drugs are used as in patients with permanent pacemakers as in patients without pacing. More frequent prescribing of beta-blockers was associated with prevention of development of possible pacemaker-induced arrhythmias. More rare appointment of acetylsalicylic acid and statins are linked to the lack of attention to their therapeutic support.

2. Prescribing frequency of most used in patients with pacemakers drugs increases with QRS complex duration class, what probably reflects more severe clinical situation and a worse prognosis in these patients.

3. Patients with pacemakers in QRS complex duration classes 120-149 ms and > 150 ms are need more intensive drug therapy.

PROSPECTS FOR FUTURE STUDIES

It seems appropriate to explore the possibilities of optimization of medical support patients with implanted pacemaker taking into account QRS complex duration class.

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CLINICAL COURSE OF MYOCARDITIS IN INFECTIOUS MONONUCLEOSIS IN ADULTS

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In conducting of complex examination (clinical, laboratory, virological, instrumental) of 186 patients with infectious mononucleosis acute myocarditis was diagnosed in 50 (26,9 %) cases. In 10 % of patients myocarditis was asymptomatic but the clinical picture was veiled by primary infectious process. Drug treatment of viral myocarditis of infectious mononucleosis must include antiviral drugs (acyclovir), drugs that affect the inflammatory, autoimmune and allergic processes, restoration and maintenance of hemodynamic, metabolic drugs, symptomatic therapy.

KEY WORDS: infectious mononucleosis, Epstein-Barr virus, myocarditis, diagnostic, treatment, acyclovir

КАРДІАЛЬНІ УСКЛАДНЕННЯ ПРИ ІНФЕКЦІЙНОМУ МОНОНУКЛЕОЗІ У ДОРОСЛИХ

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При проведенні комплексного обстеження (клінічного, лабораторного, вірусологічного, інструментального) 186 хворих на інфекційний мононуклеоз гострий міокардит діагностовано у 50 (26,9 %) випадків. У 10 % хворих міокардит перебігав безсимптомно, клінічна картина була завуальована первинним інфекційним процесом. Медикаментозна терапія міокардиту при інфекційному мононуклеозі повинна включати противірусні препарати (ацикловір), препарати, що впливають на запальні, автоімунні та алергічні процеси, відновлення та підтримання гемодинаміки, метаболічні препарати, симптоматичну терапію.

КЛЮЧОВІ СЛОВА: інфекційний мононуклеоз, міокардит, діагностика, лікування, вірус Епштейна-Барр, ацикловір

КЛИНИЧЕСКОЕ ТЕЧЕНИЕ МИОКАРДИТА ПРИ ИНФЕКЦИОННОМ МОНОНУКЛЕОЗЕ У ВЗРОСЛЫХ

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При проведении комплексного обследования (клинического, лабораторного, вирусологического, инструментального) 186 больных инфекционным мононуклеозом, острый миокардит диагностирован в 50 (26,9 %) случаев. У 10 % больных миокардит протекал бессимптомно, клиническая картина была завуалирована первичным инфекционным процессом. Медикаментозное лечение миокардита при инфекционном мононуклеозе должно включать противовирусные препараты (ацикловир), препараты, оказывающие влияние на воспалительные, аутоиммунные и аллергические процессы, восстановление и поддержание гемодинамики, воздействующие на метаболизм миокарда, симптоматическую терапию.

КЛЮЧЕВЫЕ СЛОВА: инфекционный мононуклеоз, вирус Эпштейна-Барр, миокардит, диагностика, лечение, ацикловир

INTRODUCTION

Infection caused by human herpes virus Type 4 (HHV-4) or Epstein-Barr virus (EBV) takes an important place in the structure of infectious diseases of herpesvirus etiology. It is considered that from 40 to 70 % of population of various regions of the planet are EBV infected. Infectious mononucleosis (IM) is the most wide-spread infant disease which is more often diagnosed among adult population lately. Manifest forms of IM are usually clinically manifested by the triad of symptoms: fever, lymphadenopathy and tonsillitis with further affection of immune system which is characterized by long-term persistence of the virus in B-lymphocytes [1-2].

In clinical practice such forms of IM are met in which among the mentioned triad other clinical manifestations are possible, which are connected with heart affection: myo-, endo- or pericarpdites; central and periphery nervous system: meningites, meningoencephalites, mono- or polyradiculoneurites; kidneys: nephrites; grandular organs: pancreatitis or orchites, etc [3-4].

Affection of the heart muscle in IM is studied insufficiently and up to now it was considered that myocardites in patients with IM rarely develop. Though according to T.V. Tolsticova et al. [5], in examination of 47 children with IM acute myocarditis was diagnosed in 12,5 %, endocarditis – in 2,4 %, infectious coronaritis – in 37,5%, Kawasaki disease in 17,5 % of patients.

E. Stephen et al. [6] diagnosed the myocardites development in 32 % of patients with IM with typical and atypical form of the disease course. Other authors consider that heart affection can appear only in severe course of IM and can be the fatal course in the given category of the patients [7-9].

It should be mentioned that diagnostics of reactivated, latent and chronic forms of EBV-infection in clinical practice according to clinical signs as it is widely used in infections caused by herpesvirus representatives takes place not in the right time, as it is necessary to conduct modern laboratory tests for diagnosis verification which are inaccessible for many medical establishments of Ukraine. As present data of complicated IM forms frequency development with heart affection were described mostly in children, the aim of our research is the study of development frequency, clinical course peculiarities and treatment of acute myocardites in adults with IM.

OBJECTIVE

Aim of the research is diagnostics and study of development frequency, clinical course peculiarities and treatment of acute myocardites in adults with IM.

MATERIALS AND METHODS

186 patients with IM at the age from 18 to 32 (81 women and 75 men) were examined, among which in 50 (26,9 %) cases acute myocarditis was diagnosed. In this category of the patients mild form of myocarditis was diagnosed in 16 (32 %), moderate form – in 24 (48 %), severe form – in 10 (20 %) patients (fig.). According to N.D.Strazhesko and V.H.Vasilenko classification I-st stage blood circulation insufficiency was found in 25 (50 %), II «A» stage – in 8 (16 %) cases. Sorting of the patients was incidental, examination was carried out in acute period of the disease and in dynamics in process of recovery.

Complex of patients examination included clinical blood analysis, revelation of atypical mononuclears, definition of specific Ig to EBV in the way of immune-enzyme analysis (IEA), revelation of DNA by polymerase chain reaction (PCR), asparaginic and alanine transaminase activity (AsAT, AlAT), lactate dehydrogenase (LDG) and creatin-phosphatkinase (CPhK) and its MB-fraction (MB-CPhK), content of C-reactive protein (CP), tropine-I, seromucoids and fibrinogen in blood. Registration of electrocardiogram (ECG) in 12 standard abductions, heart ultrasound research (Echo-CG) and roentgenological study of thorax were carried out.

Statistic processing of the research results was carried out with the use of Statistika 6.0 for Windows (Stat Soft Inc, USA) program on personal computer with Pentium II Celeron 850 PPGA processor. Arithmetic mean (M), average quadratic deviation (σ), average error of average arithmetic mean (m) were calculated for each variation row. Estimation of average quantities differences probability (p) was carried out with the help of Student-Fisher criterion (t). Disagreement was considered reliable under $p < 0,05$ meaning. The data of the results got during the examination of this category of patients are presented in the article in the way of absolute and relative meanings.

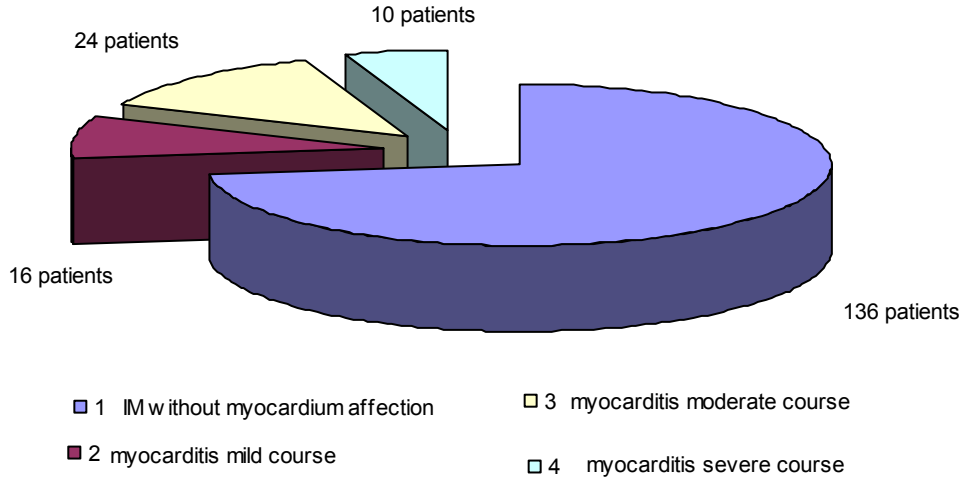

Fig. Frequensy of myocarditis occurrence in IM patients

RESULTS AND DISCUSSION

In the first days of IM the patients complained about general feebleness, headache, myalgiae, arthralgiae, ache in throat while swallowing, excessive sweating, rise of temperature to 38-39,5ºC which kept for 1-3 weeks and sometimes longer. Typical changes being characteristic features of IM were found in clinical blood analysis: moderate hypochromic anemia. In the first 2-3 days of the disease leucopenia was marked which further was replaced by leukocytosis (9-15 x 10^9/l). Content of uninuclear elements (lympho- и monocytosis) grew sufficiently and reached 50-80 % from the general number of leukocytes. The characteristic feature of IM was the presence of atypical mononuclears in blood (20 % and more) the appearance of which is typical on the 2-3 day of IM. Duration of atypical mononuclears preservation comprises in average 2-3 weeks, sometimes up to 2 months. ESR in the mentioned category of patients remained normal.

In all patients with IM EBV DNA was found in saliva and blood by PCR-method and specific immunoglobulins VCA-IgM, EA-IgG by IFA method.

In most patients with IM myocarditis developed during the first week of the disease and rarely occurred on 2-3 week. Thus, myocarditis clinical picture depended on the level of myocardium affection varying from not symptomatic course to expressed level of cardio-vascular insufficiency.

As our investigation showed among all complains of the patients with IM the complains on heart pain, dyspnea and accelerated cardiopalmus dominated under myocarditis development. Painful sensations (cardialgiae) of nagging or stabling character were found in 43 (86 %) patients and had undefined duration. Thus pain irradiation, legible connection between physical and psychoemotional tension were absent, pain was seldom cut short by nitroglycerin taking. Only in 6 patients (12 %) heart pain was cut short by sublingual taking of nitroglycerin. The latest incident is connected with the fact that a great role can belong to vascular component in mechanisms of pain appearance, which is connected with endothelium dysfunction and vasculitis development [8-10].

Complains on dyspnea at ward and tiny physical loading were marked in 23 patients (46 %). Dyspnea was often subjective and was not considered the cause of blood circulation insufficiency, respiratory rate in this case did not practically change, saturation of arterial blood by oxygen was normal.

Acceleration of cardiopalmus was the complain in 31 (62 %) cases, intermissions in heart activity were marked in 10 patients (20 %) which appeared while walking or changing the body position. 12 (24 %) patients with blood circulation of II «A» stage complained on tiny edemae of feet and ankles.

It should be mentioned that in 10 patients (20 %) the mentioned above complains were absent, and myocarditis was diagnosed during

clinical, electrocardiographic and ultrasound examination. Atypical complains of the patients with myocarditis connected with endured IM included: sweating, quick fatigability, general asthenia, sleepiness, headache, vertigo, mialgiae and arthralgiae.

Under physical examination tachycardia was found in 35 (70 %) patients, bradycardia – in 5 (10 %) and in other 10 (20 %) cases heart rate frequency was normal, heart rhythm disorders were registered in 15 patients (30 %). In patients with acute myocarditis pulse rate did not correspond the increase of temperature and remained increased both in ward and in loading. Propensity to arterial hypotonia was found in 18 (36 %) patients, thus arterial pressure data depended on the level of myocardium affection and periphery compensatory mechanisms activity. Under severe myocardium affection decrease of systolic and increase of diastolic arterial pressure were found. Under mild and intermediate myocarditis in most of the patients systolic and diastolic AP were normal.

Heart dilatation in particular on account of the left ventricle was found in 25 (50 %) patients with acute myocarditis. Heart intensity dilatation depended on the level of heart muscle affection and suffered reverse development in process of the patients recovery.

Auscultative heart changes under myocarditis are of permanent importance in physiccal examination of the patient, though differ in sufficient polymorphism. Level of these changes sufficiently depended on the process stage and severity of heart muscle affection. Muting of heart tones was usually observed in combination with pathological tones (III and IV) appearance in presence of sufficient myocardium changes and formation of, correspondingly, protodiastolic gallop rhyme and presystolic gallop rhyme. In some patients pendulum-like rhyme was defined. Weakening of the I tone and listening of the systolic noise over the apex were important symptoms of the heart muscle affection. Noise, as a rule, had weak intensity, it began immediately after the I tone, decreased in the direction to the I tone and led to the left axillary region. Regurgitation of blood into the cavity of the left auricle stipulated for the weakness of papillary muscles and prolapse of mitral valve folds is on the basis of the mentioned systolic noise.

The character of heart auscultative manifestations considerably depended on adherence of rhyme disorders and conductivity. Sometimes under associated pericardium affection the noise of pericardium friction was listened.

All mentioned subjective and objective clinical symptoms of acute myocarditis in patients with IM can mix stipulating different clinical picture. In most cases the patient does not have all symptoms described above and the clinical picture of myocarditis is defined by only some of them.

Estimation of clinical symptoms of acute myocarditis in patients with IM is made more difficult by simultaneous presence of the main infectious disease symptoms. In this connection it is often difficult to say which complains are stipulated for the main disease and which of them are connected with myocarditis, that is why laboratory and instrumental methods of investigation are widely used in myocarditis diagnostics.

Laboratory diagnostics of myocardium affections supposes the study of cardiospecific enzymes level in blood serum (MB fraction, CPhK, AsAT, LDH). Thus it was shown in some studies that activity of the mentioned enzymes authentically exceeds normal indices in less than 10% of patients in acute period of intermediate form of myocarditis [1-2, 10], which is also proved by the results of our research. So, MB-CPhK activity was increased in 7 (14 %) patients, AsAT – in 20 (40 %), LDH-1 – in 10 (20%). Increase of CRP was observed in 15 (30 %) cases, seromucoid – in 13 (25 %), fibrinogen – in 15 (30 %), tropine-I – in 5 (10 %) patients. However increase of LDH-1 and AsAT activity, content of CRP in blood, seromucoid, fibrinogen are atypical and can be stipulated for IM, intoxication, various affections of skeletal muscles, liver, lungs, kidneys, etc., which limits the use of these tests in myocarditis diagnostics under IM.

Hematological changes in patients with IM do not also reflect dynamics of the changes observed in myocardium, that is why we made an attempt to study diagnostic possibilities of instrumental research methods (ECG, Echo-CG, heart roentgenography) in myocardites detection in patients with IM.

Analysis of the received data showed that atypical ECG changes are detected in 96 % (48 patients) with infectious myocardities. Especially valuable information can be received while observing ECG dynamics. Changes of repolarization of ventricles

processes; depression or increase of RS-T segment in standard and thoracic abductions, appearance of lowered, smoothed or negative T wave in thoracic and (or) standard abductions; conductivity violations, including elongation of electric systole of ventricles (QT interval), sino-atrial, atrioventricular blockade of various extent, intraaurical and intraventricular conductivity violations, bundle of His stems blockade; various heart rhythm violations, such as sinuses tachycardia and more seldom sinuses bradycardia, pacemaker migration, auricle and ventricular extrasystole, auricle or nodal tachycardia are commonly registered. In myocarditis complicated by fibrinous pericarpditis concordent increase of S-T segment in abductions was detected where R wave is dominating; in diffuse extended myocarditis decrease of R wave voltage took place and in rare cases pathological Q-wave was registered.

During treatment while clinical improvement appears ECG changes were subjected to reverse development and came to norm in most of the patients. Low voltage of R-waves remained for a long time and heart rhythm and conductivity violations were registered.

It should be mentioned that heart rhythm and conductivity violation in separate cases of tiny symptomatic myocarditis can be the only markers of pathological process in heart muscle and demand special attention both in acute period of the disease and in the period of convalescence.

During echocardiographic research (Echo-CG) the following changes are detected in patients with acute myocarditis:

- increase of heart cavities size in 20 (40 %) patients;
- increase of left ventricle wall thickness at the expense of its edema in 20 (40 %) patients;
- decrease of emission fraction less than 50 % in 8 (16 %) patients;
- prolaps of mitral valve – in 15 (30 %) patients;
- hypokinesia zone of myocardium various segments were found in 6 (12 %) patients.

In symptomless and tiny symptomatic myocarditis Echo-CG data were normal, small increase of final diastolic volume (FDV) and final systolic volume (FSV) of the left ventricle were rarely found. In more severe cases accompanied by descent of myocardium contractility decrease of emission fraction less than 50 % and systolic index were detected, more significant increase of FDV, FSV and left auricle size. Decrease of emission fraction less than 50 % is considered a bag prognostic indication.

Separation of pericardium folium and detection of a small amount of liquid in pericardium cavity found in 6 (12 %) patients prove the development of myocarditis.

Under roentgenological (fluorographic) heart research in 20 (40 %) patients with infectious myocarditis intermediate increase of heart size was found, connected with one or both ventricle cavities widening.

In most patients with myocarditis roentgenological signs of heart chamber dilatation on the background of effective treatment decreased sufficiently or had reverse development.

The results of our study prove that in 50 patients (26,9 %) with IM acute myocarditis can develop, Epstein-Barr virus and opportunitive infection can serve its etiological signs which are connected with humoral immunity violation and active virus replication.

Thus mild course of myocarditis was characterized by the absence of heart growth and cardiac insufficiency manifestations. The course of myocarditis can be symptomless without any subjective manifestations under which heart affection is revealed only during ECG, biochemical (AsAT, MB-CPhK, troponin-I) or ECG research.

Under intermediate course growth of heart dimensions was observed, expressed ECG, Echo-CG and roengenological changes, symptoms of blood circulation insufficiency were absent or corresponded the I stage.

Cardiomegalia was typical for severe course of myocarditis, rhyme and conductivity disorder, repolarization processes disorder, increase of systolic and diastolic volumes, lowering of emission fraction to 50 % and lower, blood circulation insufficiency of the I and II «A» stage.

At present the following trends are singled out in treatment of acute myocarditis:

- etiotropic therapy;
- pathogenetic;
- symptomatic treatment of complications.

As etiotropic therapy antivirus preparations were used: acyclovir 5-10 mg/kg, intravenous infusions every 8 hours. Pathogenetic therapy included the prescription of anti-inflammatory preparations (ortofen, indometacin, ibuprofen, etc.), desensitizing remedies (loratadin, arius,

claritin), antioxidants (quercitin, ascorbiv acid, tocopherol, emoksipin), preparations improving metabolism in myocardium (trimetazidin, mexicor, corvitin, vazonat, vitamins of B group).

Symptomatic treatment included prescription on reading of antiarrhythmic preparations (nebilet, concor, ethacyzin, propafenone and cordaron); disaggregants (clopidogrel), diuretics (verospiron, gipotiazid, torasemide, etc.).

Duration of staying in bed in mild and intermediate course of myocarditis comprised in average not less than 1-2 weeks, in severe course of myocarditis the duration of staying in bed increased to 2-4 weeks with gradual broadening of the regime under constant control of cardiologist.

The prognosis of the disease depended, first of all, on spreading of heart muscle affection and peculiarities of inflammatory process in myocardium, presence of left ventricle dysfunction and severity of the disease course against the background of which myocarditis develops.

During the conducted complex therapy stable clinical improvement was observed in all patients under study, heart rhyme and conductivity came to normal, parameters of hemodynamics and the condition of electrophysiological processes in myocardium improved, the patients returned to their professional activity or studies.

Duration of the treatment course of the patients with infectious myocarditis depends on the disease severity and effectiveness of the used treatment. According to the data of morphological investigation acute myocardium inflammation in the way of lymphocytic infiltrations lasts from some weeks to some months, its duration on the basis of electrocardiographic changes comprises 1-2 months, according to the laboratory research data – not less than 1 month, according to clinical symptoms – from some weeks to some months [2-3, 5, 11]. It is supposed that inflammatory process in heart muscle continues after the reverse development and disappearance of myocarditis clinical manifestations coursing further subclinically, transforming gradually into dilated myocardiopathy [10-12]. Thus long-term treatment courses – from 2 to 6 months and sometimes more prolonged are necessary in treatment of infectious myocarditis. Course of treatment not more than some weeks is surely insufficient. It allows only to eliminate the most acute clinical manifestations, but inflammatory process in heart muscle can last subclinically up to the next aggravation, moreover EBV-infection can transform into chronic active form and support inflammatory process in heart muscle, that is why patients recovering after infectious myocarditis must keep sanitarium supervision of cardiologist and, possibly, infectionists as well, and receive antirecurrent therapy if necessary.

CONCLUSIONS

1. Acute myocarditis is diagnosed in 26,9 % of patients with infectious mononucleosis caused by Epstein-Barr virus. In 10 % of patients myocarditis can follow its symptomless pattern, the disease clinical picture can be masked by primary infectious process.

2. Clinical, laboratory (LDG-1 activity growth, AsAT, MB-CPhK and tropine-I), ECG, Echo-CG and roengenological research play a great role in myocarditis diagnostics in patients with infectious mononucleosis.

3. In the period of active virus replication conduction of virological and laboratory methods of research are necessary with the aim of infectious process dynamics control and reverse complications development.

4. Drug treatment of myocarditis in patients with infectious mononucleosis must include: antivirus preparations (acyclovir); preparations influencing the inflammatory, autoimmune and allergic reactions, restoration and support of hemodynamic, influence on myocardium metabolism, symptomatic therapy.

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Clinical case

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CLINICAL CASE OF CHRONOTHERAPY OF ARTERIAL HYPERTENSION

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A clinical case of chronotherapy of arterial hypertension is described. In patient U., according to ambulatory blood pressure monitoring (ABPM) results, 24-h average value was 145 mmHg for systolic blood pressure (SBP) and 88 mmHg for diastolic blood pressure (DBP), DBP circadian rhythm had «over dipper» pattern while SBP circadian rhythm was normal. Taking into account the daily individual BP profile the patient was prescribed antihypertensive drug lisinopril 10 mg in the morning after waking up. As a result of the treatment, after 3 months the target BP levels were achieved, but SBP and DBP pattern have been transformed into «non-dipper» ones. The treatment regimen was modified: patient was recommended daily dose of lisinopril distributed into two doses-5mg in the morningand5mg in the evening before going to bed with the subsequent control by ABPM in 3 months.

KEY WORDS: arterial hypertension, chronotherapy, ambulatory blood pressure monitoring

КЛІНІЧНИЙ ВИПАДОК ХРОНОТЕРАПІЇ ПРИ ГІПЕРТОНІЧНІЙ ХВОРОБІ

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Описано клінічний випадок хронотерапии при гіпертонічній хворобі. Пацієнтка У., середньодобовий артеріальний тиск (АТ) за даними добового моніторування артеріального тиску (ДМАТ) 145/88 мм рт.ст., порушення добового ритму діастолічного артеріального тиску (ДАТ) по типу «overdipper», добовий ритм систолічного артеріального тиску (САТ) в межах норми. Пацієнтці рекомендовано час прийому антигіпертензивних препаратів з урахуванням добового індивідуального профілю АТ: лізиноприл 10 мг вранці після пробудження. У результаті проведеного лікування через 3 місяці досягнута нормалізація АТ, однак розвинулося порушення його добового ритму за типом «non-dipper» для САТ і ДАТ. У схему лікування внесені зміни: рекомендовано дозу препарату розподілити на два прийоми - 5 мг вранці і 5 мг ввечері перед сном з подальшим контролем методом ДМАТ через 3 місяці.

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

КЛИНИЧЕСКИЙ СЛУЧАЙ ХРОНОТЕРАПИИ ПРИ ГИПЕРТОНИЧЕСКОЙ БОЛЕЗНИ

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Описан клинический случай хронотерапии при гипертонической болезни. Пациентка У., среднесуточное артериальное давление (АД) по данным суточного мониторирования артериального давления (СМАД) 145/88 мм рт.ст., пограничное нарушение суточного ритма диастолического артериального давления (ДАД) по типу «overdipper», суточный ритм систолического артериального давления (САД) в пределах нормы. Пациентке рекомендовано время приёма антигипертензивных препаратов с учётом суточного индивидуального профиля АД: лизиноприл 10 мг утром после пробуждения. В результате проводимого лечения через 3 месяца достигнута нормализация АД, однако развилось нарушение его суточного ритма по типу «non-dipper» для САД и ДАД. В схему лечения внесены изменения: рекомендовано дозу препарата распределить на два приёма - 5 мг утром и 5 мг вечером перед сном с последующим контролем методом СМАД через 3 месяца.

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

INTRODUCTION

A timely diagnosis of arterial hypertension (AH) and subsequent adequate blood pressure (BP) control can prevent the development of complications, prolongate working age and increase the life expectancy in patients with hypertension[1].Clinical studies have proven the effectiveness of BP monitoring(ABPM) both in the diagnosis of hypertension and assessment of the antihypertensive treatment efficacy [2-3].

ABPM data allow optimization the time of antihypertensive drugs administration, based on individual circadian blood pressure profile. However, in some cases, the achievement of target levels of blood pressure leads to the disruption of the circadian rhythm of blood pressure, which in turn also requires correction.

In this regard, it seems to us that a clinical case of a patient U. observed on the clinical base of our department is of great interest.

CLINICAL CASE

Patient U., female, 59 years old, complained of headaches in the occipital region on the background of increased blood pressureto160/90 mmHg, tinnitus, irritability, sometimes dizziness, flashing «flies» before the eyes.

No occupational hazards (university teacher, now retired), denies smoking and alcohol abuse. Living conditions are satisfactory; she has an active lifestyle by daily walking for 60 minutes.

She has been suffering arterial hypertension for 10 years. She occasionally takes beta-blockers, calcium channel blockers, angiotensin-converting-enzyme (ACE) inhibi-tors. At the time of admission she was taking enalapril 5mg2 times a day, without a significant effect-BP was still within the ranges 150-160/90-100mmHg according to home BP monitoring data.

Anamnesis vitae was unremarkable.

On physical examination the patient's height was 165 cm, weight 66 kg, BMI 24,2kg/m^2. Data of heart, lungs and abdomen examination were unremarkable. According to the results of laboratory tests changes in the full blood count and urinalysis were not found. Biochemical blood analysis (fasting plasma glucose level, lipid profile, serum potassium and sodium, uric acid and creatinine levels with estimation of GFR) revealed: total cholesterol plasma level of 5 mmol/L; other results were unremarkable. Results of ultrasonography of the kidneys and adrenal glands were within norm. Echocardiography revealed moderate hypertrophy of the left ventricle, ejection fraction of 64 %. 12-lead ECG was unremarkable.

ABPM was performed on the fifth day after enalapril withdrawal. The ABPM results confirmed the presence of hypertension (tab. 1-2, fig. 1). Average daily BP was 145/88 mmHg: awake BP was 150/92 mmHg, and asleep BP was 128/73 mmHg which exceeded the normal values [3]. The SBP circadian rhythm was normal (physiological reduction in SBP during the nighttime was within normal ranges) and DBP circadian rhythm had «over dipper» pattern.

Furthermore, a study of quality of life using the SF-36 revealed decline in almost all scales of the questionnaire (tab. 3).

Based on these data the following diagnosis was formulated:

Arterial hypertension II degree, stage 2. Heart failure, I stage with preserved left ventricle systolic function, I functional class. Moderate additional cardiovascular risk.

Prescribed treatment:

1. Diet low insalt, animal fat, easily digestible carbohydrates and rich in fibers.

2. Physical activities at the maintenance level.

3. Lisinopril 10mg once daily. Taking into account the individual BP profile, the patient was recommended to take the drug in the morning immediatelyafter waking up.

After 3 months due to the treatments regimen the patient's condition was significantly improved: headaches regressed, overall health status and mood were improved, the quality of life increased for 5 and more units (tab. 3).

Repeated ABPM confirmed the achievement of target BP levels (tab. 1, fig. 2). But despite the blood pressure levels normalization its circadian rhythm has been changed. Physiological «dipper» pattern of SBP and «overdipper» pattern of DBP have been transformed into«non-dipper» ones.

Table 1

ABPM indices

Indices	Baseline	3 months later
SBP, daily mean, mmHg	145	127
SBP, awake mean, mmHg	150	127
SBP, asleep mean, mmHg	128	127
SBP time index, %	83,2	30,4
Awake SBP variability, mmHg	15,1	11,9
Asleep SBP variability, mmHg	16,2	6,9
DBP, daily mean, mmHg	88	79
DBP, awake mean, mmHg	92	80
DBP, asleep mean, mmHg	73	74
DBP time index, %	76,9	51,3
Awake DBP variability, mmHg	12,5	9,2
Asleep DBP variability, mmHg	8,3	4,1
The sleep-time SBP decline, %	14,7	0,5
The sleep-time DBP decline, %	21,4	7,3
Pulse pressure daily mean, mmHg	57	48

Table 2

Hours after awakening

Indices	Baseline	3 months later
morning SBP surge value	54 mmHg	59 mmHg
morning DBP surge value	48 mmHg	51 mmHg
morning SBP surge velocity	24 mmHg/h	- 39 mmHg/h
morning DBP surge velocity	38 mmHg/h	6 mmHg/h

Table 3

Health-related quality of life (in points by SF-36 scale)

Health concepts	Items	Baseline	3 months later
physical functioning	PF	85	90
role limitations because of physical health problems	RP	50	100
bodily pain	P	100	100
general health perceptions	GH	70	82
Physical Component Summary	PCS	52,63	59,65
vitality (energy/fatigue)	VT	70	65
social functioning	SF	87,5	87,5
role limitations because of emotional problems	RE	100	100
general mental health	MH	60	40
Mental Component Summary	MCS	50,64	45,22

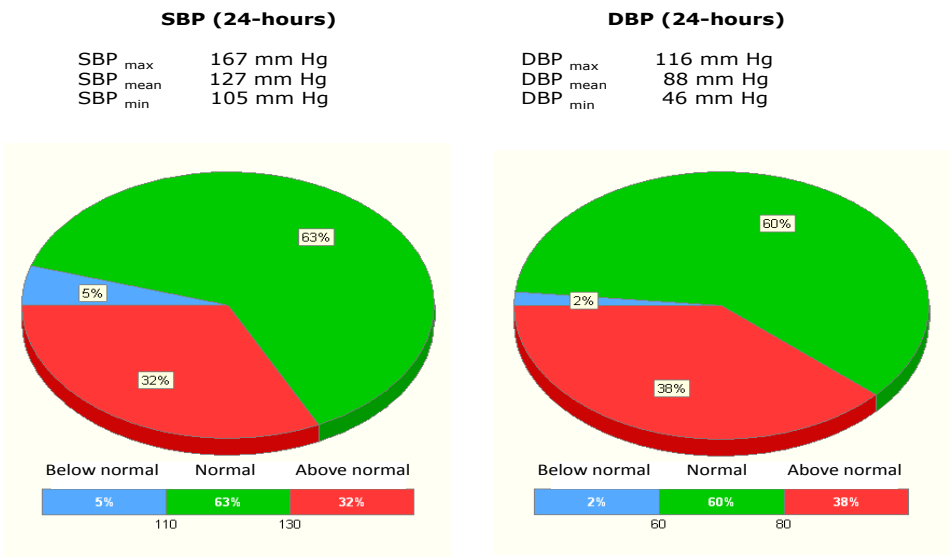

Fig.1 Average daily blood pressure at baseline

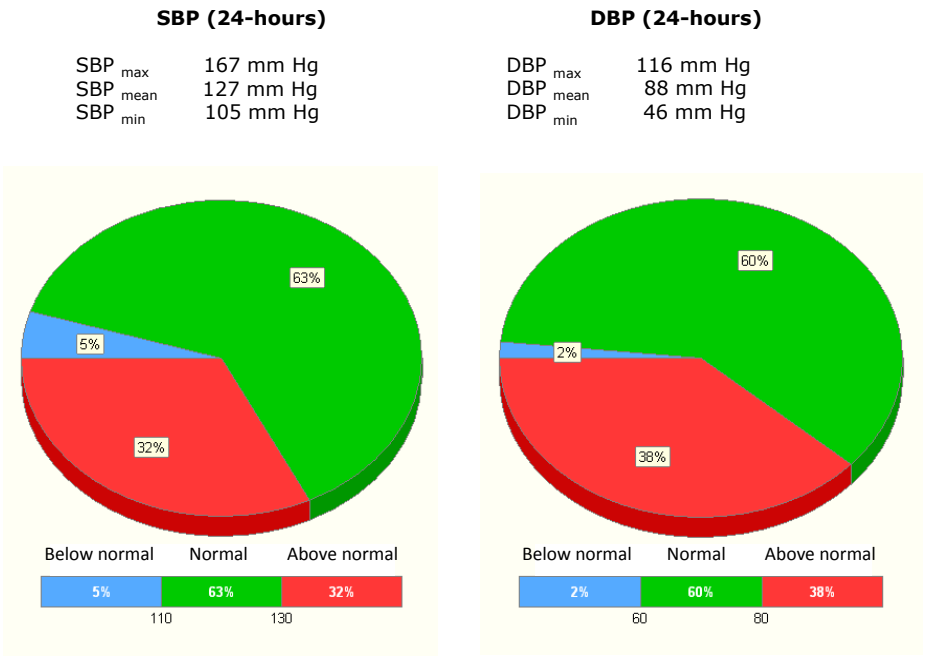

Fig.2 Average dailybloodpressure3 months after the start of treatment

For correction arisen BP circadian rhythm the patient was recommended to divide daily dose of lisinopril into two dosages: 5mg in the morning and 5mg in the evening at bedtime with the subsequent control APBM in 3 months.

The data obtained as a result of the above modification of the dosing regimen will be presented later.

Thus, in the treatment of patients with arterial hypertension, it is important not only to achieve the target BP levels, but also to preserve its physiologic circadian rhythm. ABPM allows performing comprehensive chronobiologic analysis of BP profile in patient real-life conditions that in turn allows following the strategy of chronotherapy–optimizing treatment in accordance with the obtained data about the daily BP fluctuations and variability.

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Review

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IMPORTANCE OF QTC INTERVAL DURATION IN PACING PARAMETERS OPTIMIZATION AND THERAPEUTIC MANAGEMENT OF THE PATIENTS WITH PERMANENT CARDIAC PACING

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Clinical importance of QT interval duration in patients with permanent pacemakers (PM) is discussed in the review. Physiological interpretation, methods of heart rate frequency normalization, changes under PM and role of pacing optimization parameters, reactions on medications in patients with spontaneous and stimulated rhythm, meaning for life quality and survivability of patients with permanent PM are considered.

KEY WORDS: cardiac pacing, electrocardiography, QT interval duration, QT interval dispersion

ЗНАЧЕННЯ ТРИВАЛОСТІ ІНТЕРВАЛУ QT В ОПТИМІЗАЦІЇ ПАРАМЕТРІВ СТИМУЛЯЦІЇ І ТЕРАПЕВТИЧНОМУ МЕНЕДЖМЕНТІ ПАЦІЄНТІВ З ПОСТІЙНОЮ ЕЛЕКТРОКАРДІОСТИМУЛЯЦІЄЮ

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В цьому огляді обговорюється клінічне значення тривалості інтервалу QT у пацієнтів з постійною електрокардіостимуляцією (ЕКС). Розглядається фізіологічна інтерпретація, методи нормування до частоти серцевих скорочень, зміни при ЕКС і роль в оптимізації параметрів ЕКС, реакції на медикаментозні препарати у пацієнтів зі спонтанним і стимульованим ритмом, значення для якості життя і виживаність пацієнтів з постійною ЕКС.

КЛЮЧОВІ СЛОВА: електрокардіостимуляція, електрокардіографія, тривалість інтервалу QT, дисперсія інтервалу QT

ЗНАЧЕНИЕ ПРОДОЛЖИТЕЛЬНОСТИ ИНТЕРВАЛА QT В ОПТИМИЗАЦИИ ПАРАМЕТРОВ СТИМУЛЯЦИИ И ТЕРАПЕВТИЧЕСКОМ МЕНЕДЖМЕНТЕ ПАЦИЕНТОВ С ПОСТОЯННОЙ ЭЛЕКТРОКАРДИОСТИМУЛЯЦИЕЙ

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В обзоре обсуждается клиническое значение продолжительности интервала QT у пациентов с постоянной электрокардиостимуляцией (ЭКС). Рассматриваются физиологическая интерпретация, методы нормирования на частоту сердечных сокращений, изменения при ЭКС и роль в оптимизации параметров ЭКС, реакции на медикаментозные препараты у пациентов со спонтанным и стимулированным ритмом, значение для качества жизни и выживаемости пациентов с постоянной ЭКС.

КЛЮЧЕВЫЕ СЛОВА: электрокардиостимуляция, электрокардиография, продолжительность интервала QT, дисперсия интервала QT

INTRODUCTION

Permanent cardiac pacing (CP) is one of the leading methods of bradyarrhythmia and chronic heart failure (CHF) treatment [1]. It reliably improves the life quality of the patients and reduces mortality indices [1-2], though, it always demands concurrent medical therapy both about preexisting diseases and the states induced by CP.

Despite the fact that main approaches in the using of pharmacological agents in patients with pacemaker correspond to those outside the ECS [1-2], they have a number of features. Among other factors demanding individualization of medical therapy in patients with PM the output of QT interval duration and dispersion of QT interval (QTD) outside the limits of physiological range of meanings takes an important place.

The available literature data on QT interval duration and dispersion in the patients with implanted PM and their interconnection with the use of cardiac medications are summarized in the review.

NOTION OF DURATION AND METHODS OF QT INTERVAL NORMALIZING

The QT interval is the time interval of ECG starting from the beginning of the Q wave and ending when downward knee of the T wave return to the isolines [3]. It includes QRS complex (quick depolarization and initial repolarization of interventricular septum, walls of the right and left ventricles), ST segment (repolarization plato) and T wave (final repolarization), joining them into the notion of heart electric systole.

The most important physiological determinants of QT interval duration are sex (according to Hiroto I. et al. [4] data it is greater in women than in men in norm and comprises, consequently,- 413 ± 36 ms and 401 ± 35 ms), age (according to Moss A.J. and Robinson J.L. data [5] norms of corrected QT interval in accordance with regulation on Bazett formula comprise 1-15 years - <440 ms, adult men <430 ms and women - <450 ms), as well as heart rate frequency (HRF), the rise of which in 20 bits a min decreases QT duration in 40 ms in average.

Close dependence of QT interval duration from HRF has put the task of its normalization (QTc), first successful attempts of which were taken by Bazett H.C. and Fredericia L.S. just in 1920, who suggested practically simultaneously and independently from each other similar mathematical correlation for these purposes.

Simple Bazett H.C. formula QT=0,39*RR^½ was oriented for the calculation of appropriate interval for HRF. For corrected (independent from HRF) QT interval definition a modified formula QTc=QT/(RR)^1/2 [6] was suggested. Incorrectness under high and low HRF meanings was its failing. Fredericia L.S. suggested more accurate formula - QTf=QT/(RR^1/3)^1/2 [7]. Though, it can be used only under sinus rhythm, like Bazett H.C. formula.

Sagie A. et al. suggested linear formula for QT interval duration normalization in patients with atrial fibrillation (AF) - QTc=QT+0,154*(1000-RR) according to Framingham research results [8].

There are a number of other mathematical expressions for QTc definition: Hodges M. hyperbolic (QTc=QT+a*(1/RR-1)), parabolic ($QTc=QT/RR^a$), logarithmic (QTc=QT-a*ln(RR)), Nomogram modified logarithmic ($QTc=\ln(e^{qt}+a*(1-RR))$), Sarma J.S.M. exponential ($Tc=QT+a*(e^{-RR}-1/e)$) [9].

Comparative evaluation of five methods of normalization (Bazett H.C. simple and modified, Framingham, Frederica L.S. linear and Sarma J.S.M. exponential) in 21 healthy volunteers was conducted by Molnar J. et al. [10] under computer registration of electrocardiogram (ECG). The results demonstrated absence of meaningful differences in use of any mentioned formulas as well as their insufficient accuracy in HRF output outside the limits of physiological range. The main conclusion is optimality of modified Bazett H.C. formula for QTc interval duration definition under standard 12-channel ECG.

The problem of QT interval duration normalization in patients with PM first raised more than 30 years ago by Milne J.R. et al in 1981 [11]. They explained inaccuracy of Bazett H.C. formula in patients under increase of ventricular rate (VR) on the background of right ventricle (RV) stimulation by influence on QT interval duration not only by VR, but also by sympathetic tonus.

Chiladakis J. et al. conducted a series of studies [12-13] on optimal method of QT normalization definition to VR in patients with dual chamber PM. In work [12] they studied various methods of QT interval normalization

(Bazett H.C., Frederica L.S., Sagie A.-Framingham, Hodges M. and Nomogram formulas) on 123 patients with DDD PM in groups with lengthened and normal QT interval duration under VR 60, 80 and 100 bits per min. Bazett H.C. formula showed optimal variability of QTc dependence of QT interval duration from VR in both groups, Hodges and Nomogram formula demonstrated the lowest QTc level of dependence from cardiac cycle duration. Methods of QT normalization in patients with medically determined lengthening of QT interval duration on the background of double-chamber stimulation were studied in [13]. Hodges M. and Nomogram formulas preferred to Bazett H.C. formula under VR meanings lower than 60 bits a min on the background of PM.

Common unambiguous solution about optimal method of QT interval duration normalization in patients with permanent PM is absent till now. Probably the task will be solved by QT-TENDENCY multicenter randomized study began with this purpose in March 2012 [14].

QT interval dispersion (QTD) is the change of QT interval duration from one cycle to another in one ECG lead or in various leads during the same cardiac cycle. Increase of QTD reflects the homogeneity of the process of ventricles myocardium repolarization and is one of the most important predictors of electrical instability of myocardium and increasing of ventricular arrhythmia development and sudden cardiac death (SCD) risk [15].

PROGNOSTIC SIGNIFICANCE OF QT INTERVAL DURATION IN PATIENTS WITH PACEMAKERS

Lengthening of QTc interval duration in patients both with permanent PM and without it is an important predictor of serious rhythm violations which can lead to SCD.

Solti F. et al. [16] recorded episodes of ventricular tachycardia in 11 from 12 patients with right ventricular stimulation and QT interval lengthening of stimulated complexes, which they connected with the response on early ventricular impetus under refractory period shortening.

In Prochnau D. et al. study [17] proarrhythmogenic role of QTc lengthening was demonstrated in 127 patients with severe refractory to CHF medication therapy and lengthening of QRS complex > 130 ms after biventricular (BiV) implantation of PM for cardioresynchronization therapy (CRT). In the group with registered episodes of ventricular tachyarrhythmia during 24 months after the set implantation (42 episodes in 35 patients) QTc interval duration was greater (505 ± 55 ms) than in the group of patients without arrhythmia episodes (486 ± 44 ms).

In 2013 г. Tayeh O. et al. [18] published the identical results having established a great QTc interval duration in patients with ventricular arrhythmias episodes against patients without arrhythmic events (527 ± 63.29 against 496.95 ± 45.2 ms), which proved prognostic signifycance of QTc interval in patients with CRT.

INFLUENCE OF PERMANENT PM ON QT AND QTC INTERVALS DURATION

Influence of permanent CP on QT interval duration was first described by Milne J.R. et al in 1981 [11] on 19 patients with constant right ventricular (RiV) stimulation and increase of ventricular rate (VR) after implantation not less than 50 bits a min. Metering of QTc interval duration of spontaneous and stimulated rhythm was done in all the patients which demonstrated shortening of the prolonged in rest duration of QTc after physical loading trial. The authors of the study paid attention that QTc interval duration was determined not only by VR but also by sympathetic tonus which influenced the accuracy of its estimation under the use of Bazett formula, though better normalizing criterion was not suggested. The main conclusion is that new physiological PM providing shortening of QTc interval duration but not only the syndromes of pathological repolarization correction are needed.

The same year Rickards A.F. et al [19] presented the estimation results of QT interval duration on the background of trial with increasing physical loading on 25 patients with frequency adaptive atrial PM which did not demonstrate on its background the expected essential shortening of QT interval. The result was the conclusions about the necessity of PM creation in which the stimulated rhythm frequency control is reached considering QT interval duration regardless atrial activity.

In Lelakowski J. et al [20] study the reaction of QTc interval duration in 30 patients with VVIR PM and in 6 and 24 months after radiofrequency ablation of atrio-ventricular junction (RFAVJ) regarding refractory to therapy atrial fibrillation (AF) was absent.

Correlation in RR and QTc intervals duration in 9 patients with PM in VVI mode with preserved function of sinus junction under making of stress test was studied by Oda E. et al. [21]. Authors explain the found variability of correlation degrees (in 2 patients – good (r = +0.816 and +0.897), in 4 – satisfactory (r = +0.672, +0.615, +0.615 and –0.669), in other 3 – weak (r = +0.494, +0.467 and –0.424) by individuality of sympathetic tonus influence on QTc interval duration.

Zabel M. et al [22] demonstrated direct verified dependence between QTc interval duration and VR of stimulated complexes at rest and after physical loading on 35 patients with single-chamber atrial stimulation.

Negative influence of BiV PM on ventricles repolarization was first described by Medina-Ravell V.A. et al. [23] in 2003 on the example of 29 patients with CHF, in which QTc interval duration was detected as well as transmural dispersion of repolarization (TDR) on the background of RiV endocardial stimulation, BiV stimulation and left ventricular epicardial stimulation. BiV stimulation alongside epicardial left ventricular (LV) stimulation was associated with lengthening of QTc interval duration and increase of TDR. The fact of early ventricular extrasystole appearance in 4 patients on the background of BiV stimulation and LV epicardial stimulation was explained by increase of transmural early postdepolarization which is in favor of arrhythmogenic effect of stimulation in the mentioned modes. Influence of epicardial LV stimulation on repolarization was experimentally proved on rabbit myocardium by the researchers.

Fish J.M. et al. [24] studied possible connection between QT interval prolongation and TDR increase as well as risk of arrhyth-mias development with the change of active-tion direction in the wall of stimulated LV in experiment on 12 specimens of dogs' myocardium. Under dislocation of electrode from endocardium to epicardium QT interval duration increased 297,6 ± 3,9 ms to 314,0 ± 5,7 ms and TDR - from 35,5 ± 5,2 ms to 70,3 ± 6,2 ms, which authors explained by delaying of potassium channels conduction under extremely quick activation closer to epicardium. In accordance with this, to their mind, fluttering and fibrillation of ventricles can be induced by epicardium, but not endocardium stimulation.

Interconnection between BiV stimulation and QT interval duration in 176 patients with ischemic and non-ischemic cardiomyopathy and CHF of II-III functional classes (FC) according to New York Heart Association (NYHA) with average EF = 24 ± 9 % were studied by Bhatia A et al. [25]. QT interval duration was measured before and after 30 min, 24 hours and 1 month of BiV PM implantation. The results demonstrated statistically significant lengthening of QT interval duration from 445 ± 32 ms to 470 ± 34 ms on the background of BiV PM.

The results of potential proarrhythmogenic CRT effect were demonstrated in the work by Tayeh O. et al. [18]. In 75 patients on the background of BiV PM and spontaneous rhythm QT interval duration was measured and episodes of ventricular arrhythmias were fixed. Increase of QTc interval duration was demonstrated in all the patients after CRT (from 476.2 ± 41.6 to 498.9 ± 50.8 ms), as well as greater meanings of QTc interval duration among the patients with ventricular arrhythmias episodes (527 ± 63.29 against 496.95 ± 45.2ms). Lengthening of QTc interval duration on the background of BiV PM was a predictor of ventricular arrhythmias develop-ment.

Bai R. et al. [26] compared QT interval duration on the background of RiV endocardial, LV epicardial and BiV stimulation in groups of patients without structural heart changes (15 patients) and with CHF (21 patients). The results also demonstrated the increase of QT interval duration which, however, was observed only in CHF group, it did not sufficiently differ in stimulation modes.

QTc interval duration was defined in 14 patients with CHF on the background of sinus rhythm, atrium-synchronized stimulation of RiV apex, LV epicardium and BiV stimulation in the work by Harada M. et al. [27]. The results demonstrated the increase of QTc interval duration in 10,2 % under stimulation of RV apex and in 26,1 % under LV epicardial stimulation. The fact of the absence of changes of QTc interval duration in patients with BiV stimulation pointed on minimal proarrhythmogenic effect of the given mode.

In the work by Berger T. et al. [28] the increase of QTc interval duration was described (112 ± 12 % and 114 ± 14 % consequently) in 25 patients with implanted CRT and complete left bundle branch block (LBBB) in regimes of left ventricle and right ventricle

stimulation and absence of its changes under both ventricles stimulation (99 ± 12 %).

Local QT interval duration (in LV, RiV areas and interventricular septum area) and its connection with global QT interval duration of spontaneous and stimulated complexes were studied by Douglas R.A. et al. [29] on the example of 52 patients with BiV PM. The results demonstrated the decrease of global duration of QT on the background of BiV stimulation. Local QT interval duration did not differ in all areas before and after implantation as well as QT interval duration in LV and RV areas, only in the middle area it was less on the background of BiV stimulation. Under global QT interval duration decrease absence of local changes is connected with possible absence of positive influence of CRT on ventricles repolarization in these areas.

Possibility of QT interval duration decrease under CRT was demonstrated by Samir S. et al. [30] on 33 white rabbits, divided into three equivalent groups. In one group single-chamber RiV PM were implanted, in another - BiV PM, the third group served as a control (false operated). In 4 weeks after the operation increase of QT duration was found in RiV group of stimulation from 159 ms to 174 ms and decrease – in BiV group of stimulation group from 174 ms to 156 ms. The results demonstrated advantages of BiV stimulation connected with the decrease of QT interval duration as a risk marker of ventricular arrhythmia development.

Dilaveris P. et al. [31] studied QT interval duration in 70 patients with CHF and syncope episodes or ventricular tachycardia (VT) in case history with implanted biventricular stimulators – cardioverters - defibrillators (BiV-ICD). In a year of ECG investigation maximal and minimal meanings of QT interval duration decreased and did not reliably differ in the patients group with ICD activation episodes during the study (38,6 %).

In their work Scott P.A. et al. [32] demonstrated absence of QTc interval duration changes in 43 patients under BiV with endocardial transseptal LV stimulation, under stimulation of only coronary sinus and under epicardiac LV stimulation.

Ventricle stimulation from some points as possible solution of the problem of repolarization violations under CRT was described in 2013 in the work by Ogano M. Et al. [33]. Patients with CHF of II-IV FC according to NYHA and EF ≤ 35 % and QRS complex duration > 120 ms after implantation by traditional CRT with biventricular stimulation (BiV) - 36 cases and CRT with triple site stimulation (Tri-V) (1 electrode – in RV, 2 electrodes – in LV) - 22 cases were studied. During the research period in 3,5 years QTc interval duration decreased in 14,1 % in BiV group and in 23,6 % - in Tri-V CRT group, ventricular arrhythmias were observed in 14 (39 %) cases in BiV group and in 2 (9 %) cases in Tri-V CRT group. The received results pro-ved the improvement of repolarization para-meters and antiarrhythmic effect Tri-V CRT.

INFLUENCE OF PERMANENT CP ON QT INTERVAL DISPERSION

Dispersion of normalized QT interval QT (QTcD) is not less important than QTc interval duration prognostic factor of ventricles arrhythmias development. In the work by Zabel M. et al. [22] absence of correlation of QTcD stimulated complexes with HRF at rest and after physical loading on 35 patients with single-chamber atrial stimulation were presented.

In Demir A.D. et al. [34] study QTcD was also defined in patients with atrial stimulation in groups: control group with intact coronary arteries (13 patients) and with ischemic heart disease (IHD) (12 patients - affection of one vessel, in 16 – affection of two vessels and in 14 – affection of three vessels). The results demonstrated absence of QTcD reaction on atrial stimulation in control group (43.4 ± 8.1 and 49.3 ± 9.5 ms), increase in the group of one-vessel affection from 46.1 ± 8.1 to 74.3 ± 7.7 ms, in the group of two-vessel affection - from 48.5 ± 10.4 to 93.8 ± 22.1 ms and in the group of three-vessel affection - from 49.7 ± 13.6 to 128.5 ± 31 ms. The main conclusion is that QTcD of stimulated rhythm depends on coronary disease.

Lelakowski J. with colleagues made a series of studies published in [20, 35-37] on the patients with implanted PM dedicated to the influence of various diseases and changes of functional indices connected with them on interconnection of stimulation parameters with QTD. In the work [35] in 60 patients with DDD PM QTD and heart stroke volume (SV) in DDD stimulation mode were estimated and also in a day in VVI stimulation mode with various variants of programmed AV-delay.

Patients were divided into two subgroups with IHD, arterial hypertension (AH) and their combination. Increase of QTD was associated with SV increase, mode of VVI stimulation, presence of IHD and AH. Direct inter-connection between QTD and hemodynamic status of the patient as well as possibility of QTD optimization by way of stimulation mode and AV-delay in patients with HID and/or AH became the main conclusion of the study. In the work [36], left ventricle myocardium hypertrophy (LVMH) and control according to the same protocol QTD and AV-delay were estimated in 34 patients with PM in subgroups of post-infarct cardiosclerosis (PICS) In PICS and LVMH groups in comparison with control group direct correlation between QTD and SV was demonstrated which was further used for the choice of optimal AV-delay with QTD decrease on the background of PM. In the work [37] direct connection between QTD increase and EF decrease was demonstrated in 34 patients in subgroups with ejection fraction (EF) < 50 % and > 50 % under single-chamber stimulation in VVIR mode after radiofrequency catheter ablation (RFCA) concerning atrial fibrillation in modes of stimulation frequencies decrease from 80 to 40 per min under estimation of QTmin, DeltaQTm (QTm-40 – QTm-80), QTmax, DeltaQTM (QTM-40 – QTM-80), QTD and AQTD (QTD-40 – QTD-80). QTD changes in the study [20] were absent in 30 patients with VVI PM in 6 and 24 months after radiofrequency ablation of atria-ventricular junction (RFAVJ) of refractory to therapy AF.

Data of CRT influence on QTD are also contradictory. In Chalil S. et al [38] study QTcD was registered before implantation and in 48 months after CRT implantation in 75 patients with resistant to medical therapy CHF (III-IV FC according to NYHA). QTcD increased on the background of CRT in 47 % of patients among which reliable increase of arrhythmias development was demonstrated.

Absence of QTD reaction on the background of QT interval prolongation under BiV stimulation was demonstrated in Pastore C.A. [39] study in 50 patients with BiV PM implanted concerning CHF with III-IV FC according to NYHA and complete LBBB.

Dilaveris P. et al [31] demonstrated absence of QTD changes in 70 patients with CHF and syncope episodes or VT in case history with implanted BiV-ICD. In group of patients with ICD activation episodes (38,6 %) no QTD statistically significant differences were observed during the study.

In the work by Harada M. et al. [27] QTcD was defined in 14 patients with CHF on the background of sinus rhythm, atrium synchronized stimulation of RV apex, LV epicardium and BiV stimulation. Increase of QTcD in 66,5 % cases under LV epicardial stimulation and QTcD absence of changes in patients with BiV stimulation in comparison with sinus rhythm proved about low proarrhythmogenic CRT effect.

A number of studies demonstrated the decrease of QTD after CRT PM implantation. Thus, Santangelo L. et al [40] described QTD and TDR under BiV stimulation in the group of 50 patients with dilatational cardiomyopathy and expressed atrio-ventricular, intra- and interventricular dyssynchrony. The study demonstrated a reliable decrease of ventricular repolarization heterogeneity indices: QTD and TDR on the background of BiV stimulation in comparison with sinus rhythm.

Possibility of QTcD decrease under CRT was also described by Scott P.A. et al. [41], who compared QTcD reaction under BiV with endocardial transseptal LV stimulation under stimulation of only coronary sinus and under epicardial LV stimulation in 43 patients. In group of endocardial transseptal LV stimulation (7 patients) reliable QTcD decrease was received (-45.2 ± 35.6) against the group with coronary sinus stimulation (28 patients), in groups with epicardial stimulation and under coronary sinus stimulation they did not essentially differ statistically. According to the study results the conclusion about the decrease of arrhythmias development risk was done under LV electrode setting into transseptal area in patients with CRT.

Frommeyer G. et al. [42] studied the influence of amiodarone on QTD and activity potential duration (APD) as indices of proarrhythmogenic potential in the model of stimulator-induced CHF. 35 rabbits with CHF caused by PM and 34 false-operated rabbits were divided in experiment into 2 groups: in 37 cases amiodarone was infused in dose 50 mg/kg a day, the rest of them got the infusion of sotalole in dose 50-100 mg/kg. ECG in 6 weeks demonstrated absence of QTD increase under amiodarone infusion in both groups and APD increase in group of false-operated rabbits; QTD increase in +29 ms in

groups with CHF and APD – in both groups with sotalol infusion. Effects of amiodarone were explained by the absence of triangle configuration of activity potential characteristic for sotalol and activation of the III quick phase of repolarization which testifies in favor of low proarrhythmogenic potential of amiodaron under CHF.

Because of a great number of patients who are «non-responders» to CRT a possibility of CRT response prognosticating was studied before BiV implantation of the sets with the help of QTD definition. Hina K. et al. [43] studied the connection between QTcD of spontaneous rhythm and clinical improvement in 26 patients after CRT implantation. Absence of CHF EF decrease according to NYHA during 3 months (8 cases) was considered as absence of clinical improvement on CRT. Increase of QTcD in group of non-responders proves its high significance under prognosticating of clinical response on CRT before implantation.

In 2012 Timineri S. et al. published the data of the study [44], where FC of CHF according to NYHA, tolerance to physical loading in test with 6-minute walking in 53 patients with CRT in groups with QTcD > 60 ms and QTcD ≤ 60 ms spontaneous complexes, QRS and QTcD complexes duration, indices of echocardiography (LV ejection fraction (EF), finally-diastolic size (FDS), intra- and interventricular dyssynchronia before and after cardioresynchronizing set implantation were registered. In QTcD > 60 ms group in comparison with QTcD ≤ 60 ms group in a year after implantation a reliable increase of CHF FC according to NYHA, LV EF, FDS and intraventricular LV desyncronia, decrease of tolerance to physical loading in test with 6 minute walking were observed. In accordance with these data, QTcD as an addition to QRS complex duration is an important index in choice of patients for CRT.

PERMANENT CP UNDER INITIALLY LENGTHENED QT INTERVAL DURATION

The problem of ECS implantation under initially increased QT interval duration (congenital and acquired forms of lengthened QT syndrome (LQT)) was first described in 1981 by Weber H. et al. [45] on the example of 12 patients from 3 families with congenital form of LQT syndrome. Atrial single-chamber PM was set in 4 patients with sinus bradycardia and syncopal states, the rest patients received beta-adrenergic receptors blockers therapy. Test with physical loading in patients with PM demonstrated the increase of average QTc interval duration to 540 ms on the background of loading in comparison with 430 ms in patients with LQT medical therapy. Episode of ventricular tachycardia in one of the patients on the background of CP was due to hypersensitivity of conductivity system to sympathetic tonus in the given group.

The results of one of the most essential studies of congenital LQT syndrome were published by Garson A. Jr. et al. [46] when in 281 child with LQT syndrome beta-adrenergic receptors blockers therapy caused the development of atrio-ventricular blockades in 5 % of cases demanding PM implantation. In 5 % cases more the necessity of cardioverters – defibrillators implantation aroused in connection with syncopal states and episodes of SCD, including 8 % of cases in the subgroup of QT > 600 ms interval duration.

Influence of constant CP on initially increased duration of QT interval under acquired LQT syndrome with Morganji – Adam – Stocks (MAS) syndrome in 8 patients with stimulation in AAI and DDD modes on the background of beta- blockers therapy was described in the work by Eldar M. et al [47]. QT interval duration was estimated in connection with syncopal states episodes. During 35.1 ± 18.9 months of therapy QT intervals duration shortened from 534.4 ± 51.4 to 425.6 ± 18.9 ms, thus, one patient demonstrated syncopal state on the background of hyperventilation and another patient revealed giddiness which did not repeat after exchange of AAI to DDDR PM. The study results demonstrated the effectiveness of LQT syndrome therapy with reliable decrease of QT interval duration by permanent PM method in connection with beta-adrenergic receptors blockers therapy.

Pinski S.L. et al. [48] estimated minimal frequency of stimulated rhythm, preventing TdP development in 18 patients with permanent PM under initially increased QT interval duration and ventricular flutter-fibrillation (torsades-de-pointes (TdP)) in case history. 7 TdP episodes were registered under stimulation frequency 55 ± 11 bits per min and 1 episode - under 63 ± 13 bits per min frequency. No episode of arrhythmia of TdP type was

registered under frequency > 70 bits per min, which proves in favor of its protective effect as base stimulation frequency in patients with initially lengthened QT interval.

ROLE OF QT INTERVAL DURATION FOR AV-DELAY CORRECTION UNDER PERMANENT CP

The role of QT interval duration of stimulated complexes in the choice of optimal AV-delay in patients with dual-chamber PM was studied in the series of trials by Ishikawa T. et al. [49-51]. In [49] QT interval duration and LV EF under graded increase of AV-delay in 30 ms, beginning with 90 ms was estimated in 12 patients with PM in DDD mode. The same increase of QT interval duration was observed on the grade with the greatest EF (increase from 440 ± 40 to 456 ± 39 ms). In [50] QT interval duration, LV EF and pulmonary artery jamming pressure (PAJP) under various degrees of AV-delay were estimated in the same way in the group of 10 patients with stimulation in DDDR mode. The results demonstrated maximal increase of QT interval duration (from 346 ± 60 to 353 ± 62 ms) under AV-delay with the greatest EF and minimal PAJP. In [51] 13 patients with DDDR PM with sensing transducer of QT interval duration were examined according to the same protocol. All patients demonstrated decrease of QT interval duration and LV EF both under decrease and increase of automatically defined optimal AV-delay. The series of trials demonstrated reasonability of optimal AV-delay existence with the help of QT interval duration sensing.

SENSING OF QT INTERVAL DURATION FOR PM RATE ADAPTATION

Necessity in rate-adaptive PM with sensing of QT interval duration creation was first described in 1981 in the work by Rickards A.F. et al. [52] in connection with the absence of sufficient shortening of QTc interval on the background of loading and VR in the given group of patients.

First studies of automatic sensing efficiency of QT interval duration for PM rate correction were published practically simultaneously in 1985 by Fananapazir L. et al. [53] and GoicoleadeOro A. [54]. In the work [53] sensing efficiency of QT interval duration for VR correction were studied in 13 patients with rate adaptive PM. Tolerance to physical loading was defined with the help of treadmill-test under frequency by QT interval duration sensing under atrio-synchronized stimulation (in DDD mode) and asyncronized stimulation (in VOO and VVI modes). Increase of tolerance to physical loading in patients with rate adaptation of PM in comparison with asyncronized mode, which, however, reliably did not differ from the identical one under atrio-syncronized stimulation, indicated at physiology of CP with sensing of QT interval duration for PM rate correction. In [54] tolerance to physical loading on early and distant post-operative period in groups after single-chamber (9 patients) and dual chamber (10 patients) PM implantation with QT interval duration sensing for VR correction was studied. Treadmill-test was made under VVI mode and under rate adaptation in both groups in 1-3 months and after 10-24 months. The results also demonstrated the same reliable improvement of tolerance to physical loading in groups of single- and dual chamber PM in patients with rate-adaptive sets and QT interval duration sensing.

Bloomfield P. et al. [55] described the experience of five-year observation of 8 patients with implanted rate-adaptive PM with QT interval duration sensing. Increase of tolerance to physical loading and satisfactory rate adaptation in comparison with fixed rhythm was observed in 5 patients who needed no correction of stimulation parameters in the study period. One patient needed the increase of basic stimulation rate during 5 years of study because of CHF development after acute myocardium infarction endurance, after reprogramming tolerance to physical loading under rate adaptation was reliably higher. The received data prove the reliability of QT interval duration sensing for rate adaptation in patients with long-term CP.

With the aim of greater physiology of PM rate adaptation various algorithms of QT interval duration sensing took root. The study carried out by Baig M.W. et al [56] describes the efficacy of linear and non-linear algorithms of QT interval duration sensing for stimulated rhythm adaptation to physical loading in 11 patients with PM. HRF increase, tolerance to physical loading, oxygen saturation (SaO2) were estimated in a month after every algorithm programming. Non-linear algorithm of QT interval duration sensing was associated with VR less increase time in 10 bits per min,

less rhythm fluctuations, besides tolerance to physical loading, SaO2 and correlation of VR to SaO2 did not differ under various algorithms. Non-linear QT interval duration sensing algorithm in rate-adaptive PM was presented as more physiological, though its programming did not solve the problem of stimulation rate decrease at the beginning.

The next stage for the improvement of stimulated rhythm frequency regulation as a response on physical loading was automatically dual sensing of physical activity and QT interval duration. Connelly D.T. [57] described in 1993 the results of the first 90 implantations of single-chamber stimulators with two sensing introducers programming independently, consequently, according to physical activity level and QT interval duration. In a month after implantation a sample with physical loading was done which demonstrated more gradual increase of VR in response to physical loading in sensing group with two transducers versus sensing group with physical loading introducers. Dual sensing, besides, excluded pressure factors, PM body vibration, which indicated its essential preferences.

Efficacy of automatic dual sensing of physical loading and QT interval duration were studied in the work by Lascault G. [58] on the example of 12 patients after PM implantation considering full AV-blockade in control group with normal sinus rhythm. HRF of spontaneous and VR of stimulated rhythm with sensing of only physical activity and dual sensing under various levels of treadmill-test loading were registered in a month. VR with dual sensing on the stages of physical loading was identical to sinus rhythm and greater than under sensing of only physical activity which proved sufficient physiology of PM rate adaptation with automatic dual sensing of physical activity and QT interval duration.

INFLUENCE OF MEDICAL THERAPY ON QT INTERVAL DURATION AND QTD IN PATIENTS WITH SPONTANEOUS AND STIMULATED RHYTHM

B01A A Anticoagulation and B01A C antiplatelet therapy

Anticoagulants do not usually influence QT interval duration.

Radhakrishnan M. with colleagues [59] described in 2006 the case of QT interval lengthening in a patient with intracranial aneurism which was connected with heparin-stimulated hypocalcaemia. Its correction caused its normalization. Further influence of heparin therapy on LQT duration was not studied.

The data of connection between K vitamin antagonists preparations taking and increase of QT interval duration were not earlier described in literature.

As for modern anticoagulants Morganroth J. et al. [60] found no essential changes of QTc interval duration in 96 patients on the background of betrixaban in dose 80 mg and 140 mg (therapeutic and supertherapeutic dose, consequently) in 1, 2, 3, 4, 5, 6, 8, 12, 16 and 24 hours after taking.

Similar results were received by Ring A. et al. [61] in respect of dabigatran etexilate in doses 150 mg and 600 mg (therapeutic and supertherapeutic, consequently) were studied in 40 healthy people. According to QT interval duration in 1,5 and 3 upper boundary of trust interval comprised 1,4 ms - for the group with therapeutic dose and 1,3 ms – with supertherapeutic dose (0,9 value level).

Effects of antiplatelet therapy on QT interval duration were estimated in a big randomized multicenter LANCELOT ACS trial [62]. In 603 patients with acute coronary syndrome and/or high cardiovascular risk, taking a new antiplatelet atopaxar, dose-dependent lengthening of QT interval duration was presented which reached reliable value ($p = 0,05$) in high doses groups (200 mg a day) in comparison with groups of acetylsalicylic acid therapy and group of dual antiplatelet therapy (acetylsalicylic acid and tienopiridon derivatives). The frequency of bleeding was demonstrated the same in both groups.

Anticoagulating and antiplatelet therapy in most of the patients after PM implantation as a factor of QT interval duration lengthening as well as its influence of QTD in all the patients were not earlier studied.

C01A Cardiac glycosides

In cardiac glycosides group digoxin is the only preparation used in modern practice [63-65]. Its influence studies on QT interval duration demonstrate contradictory results [66-73].

Saner H.E. with colleagues [66] were the first who in 1988 estimated the connection between digoxin taking in average therapeutic doses and ECG parameters in 97 patients with CHF without IHD clinical manifestations of ST segment shift versus 40 nondegytalized persons

of control group. The results demonstrated QT and QTC intervals duration decrease under digoxin influence.

Clinical cases of symptomatic brady-arrhythmia manifestation with QT interval duration decrease on the background of digoxin taking and hypercalcaemia, conditioned by bronchus planocellular carcinoma were described by Vella A. with colleagues [67]. After the end of digoxin taking and hypercalcaemia correction arrhythmia was cut short. The main conclusion is that proarrhythmogenic effect of digoxin under hypercalcaemia is connected with pathological shortening of QT interval, conditioned by calcium transport acceleration to carciomyocites under digoxin activity and calcium level increase in blood serum.

Guo L. et al [68] demonstrated the effect of cardiac glycosides on electric potentials of cardiomyocites on preparations received from human pluripotent sterm cardiomyocites cells (hiPSC-CMs) and preparations of Langendorff ginea pigs myocardium being in QT interval duration shortening under ouabain and digoxin effection. They saw the reason in sodium ions transport decrease and calcium ions increase in cardiomyocites which, to their mind, conditioned proarrhythmogenic activity of cardiac glycosides.

QT interval duration before and after tilt test in 20 patients with AF and CHF, 17 of which took digoxin was studied by Malik M. et al [69]. Automatic detection of QT interval duration demonstrated its shortening from 409.8 ± 11.1 ms to 401.9 ± 9.89 ms in a min and to 394.8 ± 10.0 ms in 2 min after active transition into vertical position.

Duraković Z. et al. [70], on the contrary, found no QTc interval duration correlation calculated on Bazett H.C. and Fredericia L.S. formulas with digoxin concentration in 84 patients with CHF.

QT interval duration increase on the background of digoxin therapy with TdP development on the example of classical case in 74 years old woman was described by Patanè S. et al. [71].

The alike influence of digoxin on ventricles repolarization was demonstrated according to the results of the biggest trial of medical preparations influence on QT interval duration published in 2013 by Iribarren C. et al. [72]. Digoxin was referred to the group of remedies, lengthening the QT interval from 15 to 20 ms basing on the study of 59 467 patients for the period from 1995 to the middle of 2008 in the study of 90 various remedies.

Makkar R.et al [73] demonstrated lengthening of QTC interval duration under the study of sexual differences in influence of medical preparations as well as the greater frequency of arrhythmias of TdP type on the background of digoxin therapy among women.

The data of heart glycosides influence on QT and QTD intervals duration in patients with implanted PM was not found.

C01B A-C Antiarhythmic preparation of class I

Antiarrhythmic preparations of IA class – procainamide, quinidine, disopyramide, pirmenol (classification according to VaughanWilliams, 1971) lengthen repolarization and refractory period duration through decrease of potassium and sodium flow in cardiomyocites [74].

Reiter M.J. et al. [75] compared influence of procainamide and quinidine on QTc interval duration in 18 patients. The results demonstrated dose-independent increase of QTc interval duration, longer on the background of quinidine (78 ± 10 ms), than procainamide therapy (39 ± 7 ms).

Platia E.V. et al. [76] also found dose-dependent increase of QT interval duration under the study of immediate electrophysiological effects of procainamide and quinidine in 16 patients with chronic forms of IHD.

Salerno D.M. et al. [77] described anti-arrhythmic properties of pirmenol and quinidine in 18 patients with ventricular ectopic activity, which effectiveness for the first preparation comprised 88 % and for another – 50 % with average increase of QTc interval duration, consequently, to 8 ± 9 ms and 46 ± 30 ms.

QTc interval duration increase in 20 % on the background of disopyramide introduction was demonstrated by Miyamoto S. with colleagues [78] in experiment on dogs with adrenaline-induced arrhythmias.

Disopyramide influence of QT interval duration in patients with implanted PM was studied by Furushima H. et al. [79]. In group of 8 patients with initial bradycardia-dependent LQT syndrome QT interval duration was reliably greater versus the group of 5 patients without LQT syndrome and depended on HRF (451 versus 416 ms under HRF = 90 per min, 490 versus 432 ms under HRF = 70 per min). QT interval duration increase was observed in

both groups after disopyramide taking on the background of CP and was greater in patients with LQT syndrome (78 versus 35 ms).

Antiarrhythmic preparations of IB class (lidocaine, mexiletine) have minimal influence on sodium ions transport in cardiomyocites and accelerate the repolarization process activating potassium channels [80]. Owczuk R. et al. [81] demonstrated absence of QT interval duration reaction on intravenous infusion of lidocaine in 43 women during trachea intubation while in control group with inhalational narcosis and trachea intubation without lidocaine the latter increased essentially. Mexiletine is used in congenital forms of LQT syndrome therapy due to repolarization process shortening [82].

The first clinical observation of QTc interval duration shortening under mexiletine activity was published in 1995 by Schwartz P.J. et al. [83] in 6 patients with LQT3 syndrome and 7 patients with LQT2 syndrome. It was reliable in LQT3 group (535 ± 32 and 445 ± 31 ms) and unreliable in LQT2 group (530 ± 79 and 503 ± 60 ms).

Absence of mexiletine influence on mortality in distant period among new-born children with various forms of LQT syndrome was demonstrated by Chien-Chih Ch. with colleagues [84].

Arend D.J. Ten Harkel et al. [85] described absence of QT interval duration reaction on mexiletine infusion to a new-born child with LQT3 syndrome and ventricular arrhythmias which were cut short only by medical therapy and ICD implantation combination.

Gao Y. et al. [86] studied efficacy of mexiletine for hereditary Timothy syndrome therapy, which was accompanied by frequency-dependent lengthening of QT interval with average life expectancy 2,5 years. On a clinical case of 2-year old girl example decrease of QT interval duration from 584 to 515 ms on the background of the preparation taking was demonstrated.

Preparations of IC class (propafenone, flecainide) have identical activity mechanism with preparations of IA class: slow down sodium transport of cardiomyocites acting on potassium transport in less degree [87].

Stuart J. Connoly et al. [88] describing clinical pharmacology of propafenone in 13 patients marked worsening of arrhythmia course in 2 patients (15 %) and dose-dependent increase of QT interval duration.

Proarrhythmogenic potential of propafenone was studied by Femenia F. et al. [89] on the example of clinical case of 69 year old woman with arterial hypertension and paroxysmal form of ventricles fibrillation on the background of constant enalapril, atenolol, amiodarone therapy. Infusion of 600 mg of propafenone for atrial fibrillation paroxysm cupping caused lengthening of QT interval duration with atrial fluttering paroxysm development with irregular rhythm and wide QRS complex, which further transformed into ventricular tachycardia. Arrhythmia was cut short after propafenone and antiarrhythmic preparations of III class taking.

Chimienti M. with colleagues [90] demonstrated similar increase of QT interval duration and frequency of arrhythmogenic events on the background of therapy by both preparations studying the influence of flecainide and propafenone on ventricles repolarization in 335 patients.

C01B D Antiarrhythmic preparation of class III

Among antiarrhythmic preparations of III class, lengthening the action potential, repolarization process and, consequently, QT interval duration [91], amiodaron is more often used.

Problem of amiodaron influence on QT interval duration was raised for the first time in 1986 by Torres V. et al. [92]. In 33 patients who took amiodaron in doses 2,5 and 3,2 mcg/ml during 12 ± 7 months, QT and QTc intervals duration were estimated. During the study period 6 patients died because of SCD, 3 – of out-cardiac reasons and 1 – of CHF progresssing. QT and QTc intervals duration increased in all the patients on the background of amiodaron therapy besides it was reliably greater in SCD group, though, not correlating with amiodaron dose.

The reason of lower proarrhythmic potential of amiodaron in comparison with other antiarrhythmic preparations of III class, especially, sotalole, was studied by Milberg P. et al. [93]. In experiment amiodarone was infused to 8 rabbits for 6 weeks and sotalole - to 13 rabbits, increase of QT interval duration was demonstrated in both groups which was greater in sotalole group (31 ± 6 ms and 61 ± 9 ms, consequently). Less proarrhythmic amiodarone side effect was explained by lengthening of monophase activity potential (MAP) according to rectangular scheme, while sotalole lengthens MAP according to triangle scheme which is

accompanied by great lengthening of repolarization phase.

Tong K.L. with colleagues [94] described a series of clinical cases of 13 patients with medically-induces increase of QT interval duration (average meaning - 545 ms) and development of arrhythmia of TdP type, 7 of which (57 %) were caused by amiodarone.

In the greatest randomized multicenter trial on the influence of medical preparations on QT interval duration published by Iribarren C. et al. [95] amiodarone demonstrated its greatest increase - in 25,2 ms among 90 preparations.

Mattioni T.A. et al. [96] studied the possibility of long-term amiodarone taking in 12 patients after episodes of medically-induced TdP. The results demonstrated decrease of QTc interval duration in the first 7 days (from 570 ± 40 ms at the moment of TdP to 490 ± 70 ms) and increase in 3 months of therapy (to 580 ± 80 ms). QTc interval duration in 16 ± 7 months was reliably greater in the study group in comparison with control group, though frequency of repeated TdP, episodes of syncope and SCD did not differ which allowed the authors to come to a conclusion about possibility and independence of amiodarone usage in patients with episodes of medically-conditioned TdP.

Opposite point of view was demonstrated in the work by Ramy F. Ayad et al. [97] on the example of clinical case of VT with wide complexes in a woman with QT interval increase induced by taking of antipsychotic remedies. The repeated VT episode was observed on the background of amiodarone therapy after which it was invalidated. The main conclusion is that amiodarone is contraindicated under VT with medically conditioned lengthening of QTc interval duration.

In clinical case was described by Van de Loo A. et al. [98] reaction of QT interval duration was absent in a patient with sotalole-induced TdP on the background of amiodarone therapy in 3 months, though QTD was reliably less (47 ms), in comparison with sotalole therapy (77 ms), and did not differ from control without antiarrhythmic therapy (43 ms). Informativity of QTD for identification of proarrhythmic risk of antiarrhythmic preparation of III class prescription is the main conclusion of the work.

Tran H.T. with colleagues [99] described the case of amiodarone-induced TdP with QTD duration increase in more than 100 % after quinidine-induced TdP episode which testified in favor of the necessity of QTD estimation as a potential marker of TdP development on the background of amiodarone therapy in patients having quinidine-induced TdP.

Influence of amiodarone on QTD was studied by Hii J.T. et al. [100] in 38 patients having TdP induced by taking of antiarrhythmic preparations of Ia class in case history. The results demonstrated preferences of amiodarone therapy with absence of QTD reaction (49 ± 26 ms versus basic 44 ± 12 ms) and repeated arrhythmias episodes of TdP type in comparison with control group with proceeding antiarrhythmic preparations of Ia class therapy where QTD increased to 101 ± 37 ms, the repeated TdP episodes were observed in 9 patients.

Higher risk of TdP development under amiodarone therapy in women was demonstrated by Makkar R.R. et al. [73].

Cairns J.A. et al. [101] published the results of CAMIAT trial. VF and SCD development risk was estimated in 1202 patients (606 patients took amiodarone, 596 patients comprised control group) after having acute myocardium infarction for 1,79 year. The results demonstrated less frequency of arrhythmic events in amiodarone group - 25 (4,5%) in comparison with control group - 39 (6,9%), on the basis of which the conclusion about VF and SCD risk decrease on the background of amiodarone therapy in patients after acute myocardium infarction was made.

Influence of amiodarone on QT and QTD interval duration in patients with implanted PM was not earlier studied.

Combinations of amiodarone with other preparations

Shah S.A. et al. [102] compared influence of antiarrhythmic preparations of III class monotherapy (sotalole, dofetilide, ibutilide) and their combination with amiodarone on ventricles repolarization. The results demonstrated identical increase of QT interval duration in both cases, though QTD and TdP frequency were less under combined therapy which testified for its less proarrhythmic potential.

Clinical case of QT interval duration increase in 74 years old patient on the background of digoxin and amiodarone therapy was published by Bajaj B.P. et al. [103]. The appearance of weakly controlled TdP testified

in favor of possible proarrhythmogenic effect of the given combination of preparations.

A number of cardiovascular medical preparations such as metronidazole, antiretrovirus, antihistamine remedies, etc. are not recommended for simultaneous usage with amiodarone because of possible lengthening of QT interval duration and increase of arrhythmias development risk [104-108].

C03 Diuretic preparations

Diuretics indirectly influence on QT interval duration and increase of TdP risk by the way of potassium and magnesium introduction increase. Hypopotassemia and hypomagnesaemia caused by diuretics usage can aggravate the activity of other preparations increasing QT interval duration [109].

Sato T. Et al. [110] published a clinical case of TdP type arrhythmia in a woman with the decrease of potassium level of blood serum on the background of arterial hypertension therapy by thiazide diuretics.

The results of JacksonHeartStudy trial, published by Akylbekova E.L. with colleagues [111] demonstrated direct correlation between the increase of QT interval duration and taking of diuretics in 4660 African Americans.

C07 A Beta adrenergic receptors blockers

Nonselective

The most utilized preparation of the given group is sotalole. It consists of sinister rotatory isomer - 60 %, having halved beta adrenergic receptors blockers activity and halved lengthening the activity potential, primarily in account of repolarization phase and in 40 % from dextrorotatory isomer with antiarrhythmic preparations of III class activity [112].

Graff C. et al. [113] studied the influence of sotalole on QT interval duration in the group of 39 healthy people and 30 people with congenital LQT syndrome of type 2. QT interval duration increase was the greatest in the group of healthy people for all doses of the preparation: in 72 % under taking of 160 mg and in 87 % - 320 mg of sotalole.

Increase of QTc interval duration with the increase of sotalole concentration in blood serum of 15 healthy people under oral and parenteral taking was demonstrated by Somberg J.C. et al. [114].

Knudson J.D. et al. [115] did not demonstrate reliable lengthening of QTc interval duration under the study of efficacy and independence of high doses of sotalole (15 – 200 mg/m^2 a day) in 48 new-born children and 36 children under the age of 2 years old with refractory to therapy supraventricular tachycardias, thus arrhythmias control was reached in 90 % of cases.

Weeke P. et al. [116] demonstrated statistically essential increase of QTc interval duration and QTD in 541 patients with AF or atrial flutter in 2 hours and 48 hours after sotalole infusion in dose 86 ± 39 mg.

Essential increase of QTc interval duration (to 840 ms) in a patient after wrong taking of 120 mg of sotalole was described by Kukla P. with colleagues [117].

According to Iribarren C. et al. [95] data received in 59467 patients, sotalole increased QT interval duration in 15 – 20 ms.

Somberg J.C. et al. [118] demonstrated essential increase of QT interval duration in 2,5 hours after intravenous infusion of 75 mg of sotalole in 15 health /volunteers – more in women (411 ± 13 versus 438 ± 13 ms, $p < 0.001$) and less in /men (395 ± 23 versus 413 ± 27 ms, $p < 0.05$).

Influence of CP on the change of QTc interval duration under sotalole taking was studied by Tsai S.F. et al. [119]. 22 patients with implanted permanent PM (right ventricle stimulation < 10 %) took part in the trial. The results demonstrated essential increase of QT interval duration after taking the preparation on the background of spontaneous rhythm (from 431 ± 28 to 463 ± 33 ms, $p = 0.002$) and decrease – under stimulated rhythm (from 520 ± 48 to 538 ± 45 ms, $p = 0.07$).

Selective

Selective beta blockers shorten QT interval duration and are used for congenital and acquired LQT syndrome [120-121].

Efficacy and usage limitations of beta adrenergic blockers in patients with QT interval duration increase were studied by Moss A.J. et al. [122]. Reliable decrease of mortality from cardiovascular events were demonstrated in 869 patients, receiving beta adrenergic receptors blockers for 5 years, though episodes of syncope and SCD were observed in 5,7 % of cases among the patients with LQT in case history, which is comparable with control group data.

Michael Vincent G. et al. [123] also demonstrated the efficiency of beta adrenergic receptors blockers therapy in decrease of SCD risk on 216 patients with various forms of congenital and medically conditioned LQT syndrome. The authors come to the conclusion

about the absence of necessity of routine ICD implantation to all patients with LQT syndrome in condition of sufficient compliance to therapy by this class of preparations.

Silvia G. Priori with colleagues [124] described decrease of QT interval duration and cardiovascular events risk for 5 years of beta adrenergic receptors blockers preparations therapy only under LQT1 in 335 patients with various forms of congenital LQT syndrome. QT interval duration did not relatively change and syncope risk and SCD remained high (23 % and 32 %, consequently) in patients with LQT2 and LQT3.

QT interval duration under various HRF in 20 patients taking beta adrenergic receptors preparations concerning LQT syndrome of type 1 was studied by Matthew T. Bennett et al. [125]. Increase of QT interval duration (398 ms versus 391 ms; p = 0,02) after taking 5 mg of bisoprolol was observed in the group with lower HRF (< 90 bits a min), decrease (339 ms versus 349 ms; p = 0,001) – in group with higher HRF (> 105 bits a min).

Comparative estimation of LQT syndrome therapy by selective (metoprolol - 147 patients) and non-selective (propranolol - 134 patients, nadolol - 101 patients) beta adrenergic receptors blockers for 14 years was conducted by Chockalingam P. et al. [126]. The results demonstrated the most prominent shortening of QT interval duration in those who took propranolol, as well as similarly better decrease of cardiovascular events risk on the background of propranolol and nadolol therapy.

C07A G Combined alpha and beta adrenergic receptors

Mechanism of carvedilol and its new analogue VK-II-36 combining blocking activity of alpha and beta adrenergic receptors influence on QT and QTD interval duration was studied by Maruyama M. et al. [127] in Langendorff mice and rats. Shortening of initially lengthened QT interval duration, QTD decrease was in all cases connected with inhibiting of these preparations of spontaneous increase of intracellular calcium in systole which suppressed trigger activity of ventricle myocardium and thereby prevented ventricular tachyarrhythmias development.

Influence of selective and combined beta adrenergic receptors blockers on QT and QTD interval duration in patients with implanted PM was not earlier studied.

C08 Calcium antagonists

Among potassium antagonist preparations bepridil and ranolazin have maximal proarrhythmogenic effect in QT interval duration lengthening. [128-129].

Yoshiga Y. With colleagues [130] demonstrated the increase of QTc interval duration in 50 ± 8 %, QTD in 14 ± 8 % in 10 patients with resistant to therapy proximal AF on the background of bepridil taking.

Mechanism of bepridil proarrhythmogenic activity was studied by Kang L. et al. [131] on specimens of new-born white rats myocardium. The authors came to the conclusion that the preparation increases QT interval duration on account of ventricle repolarization time increase conditioned, in its turn, by calmodulin inhibiting which shortens Na (V) degradation of 1.5 alpha components of sodium receptors and increases sodium flow in cardiomyocites.

Ranolazin is an antianginous and antiarrhythmic preparation which activity is conditionned by calcium channels blockage and inhibiting of the later phase of inner sodium flow [132].

Clinical case of QT interval duration increase and arrhythmia of TdP type development on the background of ranolazin taking was described by Liu Z. et al. [133].

Koskinas K.C. et al. [134] identified comparative for both preparations increase of QT interval duration under absence of acute cardiovascular events during 48 hours of electrophysiological effects studies of ranozolin in comparison with amiodaron in 121 patients.

Influence of amlodipin on QT and QTc intervals duration in 90 patients with arterial hypertension was studied by Milovanović B. et al. [135]. The results demonstrated statistically insignificant QT interval shortening (from 391.49 ± 31.4 to 388.31 ± 35.0 ms) and QTc (from 426.94 ± 25.3 to 424.08 ± 33.7 ms) during a day after preparation taking.

In the work by Peters F.P. with colleagues [136] clinical case of QT interval duration increase from 380 to 480 ms with further ventricle fibrillation development after 20 mg of nifedipin taking sublingually in 34 years old woman with malignant arterial hypertension was described.

According to the trial eHealthMe United States Food and Drug-Administration (FDA) [137] data 93 (0,55 %) from 16 792 cases of nifedipin side effects is increase of QT interval duration.

In Redfern W.S. et al [138] trial changes of QT interval duration in dogs were studied, its reactions and cases of TdP in human on the background of 100 of various preparations taking. Nifedipin and verapamil identically increased QTc interval duration in all observations and did not influence the TdP risk.

Shortening of QT interval duration as a result of verapamil taking was described by Fauchier L. et al. [139] in 19 patients with paroxysmmal nodal re-entry-determined tachycardia without structural heart violations on the ground of which authors make a conclusion about protective effect of verapamil against TdP.

O. Erbas [140] demonstrated the decrease of QT interval duration after diltiazem taking (125 ± 4 ms) in 18 rats with cyprazidon-induced LQT syndrome in comparison with control group (160 ± 10 ms).

According to FDA data of 5791 registered cases of diltiazem side effects only in 2 (0,03 %) the increase of QT interval was found up to 2014 [141].

Interconnection between calcium antagonists taking and QT and QTD intervals duration in patients after implantation of permanent PM were not studied before.

C09 Remedies functioning on rennin-angiotensinic system

Angiotensin-transforming enzyme effect on QTc interval duration was studied by DiasdaSilva V.J. et al. [142]. Captopril was given to rats of various ages for 2-20 months. QTc interval duration was longer in adult rats in comparison with new-born ones (117+/-4 versus 64+/-6 ms, $p < 0.05$), though it decreased under captopril (71+/-6 ms, $p < 0.05$).

Bashir Y. With colleagues [143] demonstrated reliable increase of QTc interval duration from 351 ms to 358 ms after taking 25 mg of captopril in 8 patients with decreased LV function (EF < 40 %) and ventricular tachycardia, induced by programming CP.

Data about influence of remedies acting on rennin-angiotensive system on QTD QT and QTD intervals duration in patients with implanted PM were not found.

C10 Hypolipidemic remedies

Vrtovec B. et al. [144] studied QT interval duration in 80 patients with CHF, 40 of which took atorvastatin (statins group) and 40 did not take hypolipidemic preparations (control group). The fact of QT interval duration shortening in statins group after 3 months of therapy (from 450+/-30 to 437+/-29 ms) and its absence in control group (from 446+/-27 to 450+/-25 ms) testifies about antiarrhythmic effect of statins in patients with CHF. The same group of authors described shortening of QT interval duration on the background of statins therapy during a year in 114 patients after heart transplantation [145].

In Health Me United States Food and Drug Administration trial (FDA) in 256 cases (0,36 %) from 71 991 of registered side effects of simvastatin use increase of QT interval duration was observed [146].

Reaction of QT and QTD interval duration on hypolipidemic preparations taking in patients after PM implantation were not earlier reported in literature.

LIFE QUALITY OF THE PATIENTS WITH PM AND QT INTERVAL DURATION AND QTD OF STIMULATED COMPLEXES

Influence of PM implantation on the patients life quality regardless QT interval duration and QTD was studied by Manolis A.G. with colleagues [147]. The data of individual life quality questionnaire were estimated as well as CHF FC according to NYHA and LV EF before and after PM implantation and RFAVJ concerning atrial tachyarrhythmias. 46 patients (33 - in DDDR mode with function of automatic mode switch and 13 - in VVIR stimulation mode) during 6 months after RFAVJ procedure the reliable improvement of life quality was demonstrated according to the data of individual questionnaires, LV EF increase from 42 ± 16 % to 50 ± 14 %, CHF EF increase according to NYHA in 1.4 ± 0.8, only 7 patients needed medical antiarrhythmic therapy, and only 1 patient - repeated ablation.

The greatest trial in which the connection between the patients quality of life and QT interval duration and QTD in 156 patients after PM implantation and RFAVJ concerning EF refractory to therapy, was done by Ablate and Pace Trial (APT) [148]. Individual questionnaires like Health Status Questionnaire, Quality of Life Index и Symptom Checklist: Frequency and Severity were used. Besides QT interval duration and QTD, LV EF and tolerance to physical loading in test with 6 minutes walk were estimated. Improvement of life quality was demonstrated in all three questionnaires as well as improvement of

functional indices beyond QT interval duration and QTD increase in all the patients during 12 months after ECS implantation and RFAVJ.

Lelakowski J. et al. [149] studied LV EF, QTc interval duration, QTD of stimulated rhythm, tolerance to physical loading in test with 6 minute walking, the patients quality of life according to individual questionnaires SF-36, Manolis, DASI scale in 6 and 24 months after RFAVJ considering EF refractory to therapy in 30 patients with VVI ECS. The results demonstrated increase of life quality indices on all the stages according to SF-36 and Manolis scales, increase - in 6 months and decrease - in 12 months according to DASI scale. LV EF did not essentially statistically change and in 24 months decreased. Average QTc interval duration, QTD and tolerance to physical loading remained stable during the study.

MORTALITY OF THE PATIENTS WITH PM AND QT INTERVAL DURATION AND QTD OF STIMULATED COMPLEXES

Increase if QTc interval duration is associated with increase of mortality, first of all because of SCD both in patients with spontaneous rhythm and after PM implanttation.

QT interval duration as a predictor of SCD was first described by Schwartz P.J. et al. in 1978 in 55 patients after myocardium infarction (MI) [150]. The results of 7 years study demonstrated the increase of SCD frequency in 2,16 times in group of lengthened QTc interval against the group with its normal duration.

Interconnection between lengthened QTc interval and SCD risk were studied in randomized trial Rotterdam QT Project [151] on 6693 patients with registration of 12-channel ECG and 24-hour Holter monitoring. SCD frequency was 2,3 times higher in patients with increase of QTc interval duration, though differences concerned only the group with preserved systolic function (EF $\geq$ 40%). Sex, age HRF, presence of MI in case history and taking of remedies did not influence relative risks.

Connection of QTc interval duration changes in the limits of physiological range with level and structure of mortality in 7828 patients was described in randomized multicenter trial [152]. During 13,7 years in group of QTc interval duration 410 – 439 ms the results demonstrated the increase of mortality level in 2,03 times in comparison with general mortality, in 2,55 times in mortality level from cardiovascular diseases, in 1,63 times in mortality level from coronary heart disease and in 1,65 times in the level of beyond-cardiac mortality; in group of QTc interval duration 320-377 ms – increase of mortality level in1,39 in general mortality level, in 1,35 times in mortality level from cardiovascular diseases, in 1,02 times in mortality level from heart coronary disease and in 1,42 times in beyond-cardiac mortality level. The received data prove the unfavorable influence of lengthening and shortening of QTc interval on mortality level.

The increase of QTc interval duration after PM implantation is also associated with the increase of patients mortality, first of all from SCD. In the work by Dorostkar P.C. [153] SCD was observed in 24 % cases during 6.3 ± 4.6 years after implantation in 37 patients with combined therapy of LQT syndrome by beta-adrenergic receptors blockers and permanent PM. The main conclusion is the necessity of ICD sets implantation to patients with LQT on the background of beta-adrenergic receptors blockers therapy and permanent CP, especially in the early age.

Tereshchenko L.G. et al. [154] described the increase of VT development frequency and episodes of ICD activation in 69 patients with BiV-ICD in group of lengthened QTc interval and QTD increase as well as SCD frequency increase in patients with BiV sets without ICD.

Risk of VT, ventricular fibrillation (VF) and SCD development under various QTD were studied among the patients in Multicenter Automatic Defibrillator Implantation Trial (MADIT) II [155]. 817 patients with implanted ICD after ECG registration were divided into the groups of normal and increased QTD. The received numbers of VT, VF, SCD with documented episode of ICD activation were reliably greater in the group of increased QTD.

CONCLUSION AND PROSPECTS FOR FUTURE STUDIES

The survey demonstrates an important estimation of QT interval duration and QTD in pacing optimization parameters and the choice of medical therapy tactics in patients with permanent CP. Thus, the available works in this sphere are extremely few, the data about medical therapy influence are contradictory and concern generally the patients without PM.

The outlined above proves in favor of availability of further purposeful studies of clinical applications of QT interval duration and QTD in conduction of the patients with implanted PM.

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OPEN INGUINAL HERNIA REPAIR IN ADULT PATIENTS

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The review presents the frequency, anatomy, classification, diagnosis, and the most effective open methods of inguinal hernia's operative therapy in adult patients.

These findings are in agreement with the recommendations of the Ukrainian association of surgeons-herniologists and the European European Hernia Society (EHS). The article does not deal with laparoendoscopic options of hernia repair (TAPP and TEP), as they require a separate section in the anatomy of the inguinal region and endoscopic techniques' volumetric description. Besides, in Ukraine inguinal hernia repair is most frequently performed of open access that causes the topic's timeliness.

KEY WORDS: inguinal hernia, open hernia repair, Lichtenstein's operation, Shouldice's operation

ВІДКРИТА ПАХОВА ГЕРНІОПЛАСТИКА У ДОРОСЛИХ ПАЦІЄНТІВ

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Розглядаються питання частоти, анатомії, класифікації, діагностики і найбільш ефективних відкритих методів хірургічного лікування пахової грижі у дорослих пацієнтів. Наведені дані узгоджуються з рекомендаціями Української асоціації хірургів-герніологів та Європейського герніологічного товариства (European Hernia Society, EHS). У статті не наводяться лапароендоскопічні варіанти герніопластиці (TAPP і TEP) , оскільки вимагають написання окремого розділу з анатомії пахової ділянки, і об'ємного опису ендоскопічних методик. Крім того, в Україні найбільш часто пахова герніопластика виконується з відкритого доступу, що обумовлює актуальність розглянутого питання.

КЛЮЧОВІ СЛОВА: пахова грижа, відкрита герніопластика, герніопластика за Ліхтенштейном, герніопластика за Шолдайсом

ОТКРЫТАЯ ПАХОВАЯ ГЕРНИОПЛАСТИКА У ВЗРОСЛЫХ ПАЦИЕНТОВ

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В обзоре рассматриваются вопросы частоты, анатомии, классификации, диагностики и наиболее эффективных открытых методов хирургического лечения паховой грыжи у взрослых пациентов. Приведенные данные согласуются с рекомендациями Украинской ассоциации хирургов-герниологов и Европейского герниологического общества (European Hernia Society, EHS).

В статье не приводятся лапароэндоскопические варианты герниопластики (TAPP и TEP), поскольку требуют отдельного раздела по анатомии паховой области, и объемного описания эндоскопических методик. Кроме того, в Украине наиболее часто паховая герниопластика выполняется из открытого доступа, что обуславливает актуальность рассматриваемого вопроса.

КЛЮЧЕВЫЕ СЛОВА: паховая грыжа, открытая герниопластика, герниопластика Лихтенштейна, герниопластика Шолдайса

INTRODUCTION

Since Lichtenstein hernioplasty got a widespread acceptance in surgical practice, the rate of hernia recurrence has fallen substantially (from 30 % to 4-14 %) [1-3]. In addition, a large number of different autoplastic hernioplasties are performed in the national surgical hospitals, mainly because of social reasons [3]. In this context, Shouldice hernioplasty, that until recently was the «gold standard» in North America and Western

Europe, is not so widespread. According to foreign authors the recurrence rate of this surgery is 1-4 % [1-2]. In the domestic authors' opinion a technique's complexity prevents its wide dissemination. Taking into account the fact that in different countries the treatment of inguinal hernia has inhomogeneous surgical approach, in 2009 the EHS published guidelines for the treatment of inguinal hernia in adults, which fully elucidated this pathology - from diagnosis to postoperative management [1].

In March 2014 the Hernia published an updated version of these guidelines, having supplemented it with research results with a level of evidence 1 [2]. The purpose of this article is to review scientific publications with a high level of evidence and recommendations dealing with the diagnosis and surgical treatment of inguinal hernia in adults. The review does not deal with laparoendoscopic options of hernia repair (TAPP and TEP), as they require a separate section in the anatomy of the inguinal region and endoscopic techniques' description equal in length to a separate article.

STATISTICS

Inguinal hernia is one of the most common abnormalities that require an operative intervention. The inguinal hernia's share is about 75 % among the hernias of anterior abdominal wall. Nowadays, there are no accurate data on the incidence and prevalence rate of inguinal hernia. In our country the incidence of inguinal hernia is (3-4) % [1-3]. About 27 % of European men and 3 % of women undergo inguinal hernioplasty throughout life. Approximately 200,000 hernioplasties are performed each year in Europe and 800,000 in the United States [1, 3]. The risk of inguinal hernia's incarceration is (0.3-3) % during the year. In Europe a rate of postoperative lethality during planned operations is less than 0.5 %, during urgent - more than 5 % [1, 3].

ANATOMY

The inguinal region is a genetically determined weak area in the anterior abdominal wall. Anatomically, it conforms to the Fruchaud's myopectineal orifice, which is bounded superiorly and medially by the conjoined tendon and abdominal rectus muscle, laterally – by the iliopsoas muscle, and inferiorly – by the superior pubic ramus. This area is covered by the transverse fascia. This fascia splited into two regions by the inguinal ligament, which perforates by the spermatic cord / round ligament of uterus and femoral vessels. Accordingly, the abdominal wall's integrity in the area of the Fruchaud's myopectineal orifice is provided exclusively by the transverse fascia. Abdominal membrane hernial sac prolapse or preperitoneal lipoma prolapse through the orifice leads to the inguinal hernia formation.

So the transverse fascia failure which holds the abdominal membrane and preperitoneal fat is a fundamental reason leading to the inguinal hernia formation. On the one hand the weakness of the transverse fascia may be determined by constitutional and acquired causes, on the other hand- by abdominal's increasing pressure. Obliteration disorder of the abdominal space's vaginal process is one of the main constitutional causes.

RISK FACTORS

According to the metaanalysis the highest risk of inguinal hernia is associated with the following factors: smoking, family hernial history, non-obliterated abdominal vaginal process, collagen diseases, abdominal aneurysm, appendectomy or prostatectomy in past medical history, ascite, peritoneal dialysis, prolonged laboring job, chronic cough.

Such risk factors as periodic weight lifting, constipation and benign prostatic hyperplasia are not proved. The connection between smoking and aortic aneurysm is associated with a collagen pathobolism, which is common presentation sign within this population. As for prevention measures of inguinal hernia, only smoking cessation is a recommendation, effectiveness of which is proved.

CLINICAL PROFILE OF INGUINAL HERNIA

Inguinal hernia is a protrusion of abdominal contents or preperitoneal fat through the abdominal wall's defect of the corresponding region. In case when there is no pain syndrome or sense of discomfort, inguinal hernia is called *asymptomatic*. A hernia that cannot be pushed back into abdominal cavity is known as an *irreducible hernia*. People with irreducible hernias are more likely to experience a compression of hernia sac contents with the further development of ischemia, necrosis and inflammation of the surrounding soft tissues,

which is known as a *strangulated hernia*. The most dangerous accident is colon shrinkage, which can be complicated by perforation and peritonitis. According to a mechanism of intestinal incarceration there are several types of infringements – *fecal impairment* (due to large amounts of intestinal contents in the intestinal loop), *elastic infringement* (the outlet of the excess intestinal loop length into a hernial sac due to increased intra-abdominal pressure), *retrograde infringement* (the infringement in the form of «W», the intermediate loop in the abdominal cavity is infringed) and *parietal incarceration*/ *the Richter's hernia*, which was firstly described by the German surgeon August Gottlob Richter in 1778. In 1735 the English surgeon Claudius Amyand described the outlet or/and incarceration of vermiform appendix in the inguinal hernia - *Amyand's hernia*. In 1690s the French anatomist Littre described a case of identifying Meckel's diverticulum in the inguinal hernia - *the Littre's hernia* [4]. There are two basic types of groin hernias depending on the attitude of hernial sac to the elements of the inguinal canal: the *indirect* (the peritoneum prolapses around the lateral inguinal fossa and then descends to the spermatic cord's elements through the internal ring) and *direct* (the peritoneum prolapses around the medial inguinal fossa with the hernial sac's penetration into the inguinal canal, separate from the spermatic cord's elements). A *sliding inguinal hernia* - a hernia in which one of a hernial sac's walls is an organ, covered with a visceral peritoneum.

CLASSIFICATION

According to the International Statistical Classification of Diseases 10th Revision (ICD-10) there are several types of inguinal hernias.

K 40 – inguinal hernia included: bilateral, indirect, direct.

K 40.0 – bilateral inguinal hernia, with obstruction, without gangrene.

K 40.1 – bilateral inguinal hernia, with gangrene.

K 40.2 – bilateral inguinal hernia, without obstruction or gangrene.

K 40.3 – unilateral or unspecified inguinal hernia, with obstruction, without gangrene.

K 40.4 – unilateral or unspecified inguinal hernia, with gangrene.

K 40.9 – unilateral or unspecified inguinal hernia, without obstruction or gangrene.

K 41 – femoral hernia.

K 41.0 – bilateral femoral hernia, with obstruction, without gangrene.

K 41.1 – bilateral femoral hernia, with gangrene

K 41.2 – bilateral femoral hernia, without obstruction or gangrene

K 41.3 – unilateral or unspecified femoral hernia, with obstruction, without gangrene

K 41.4 – unilateral or unspecified femoral hernia, with gangrene

K 41.9 – unilateral or unspecified femoral hernia, without obstruction or gangrene

There are a large number of clinical classifications of inguinal hernia, which allows to determine a surgical approach and optimize the patient allocation resulting from the study. A classification of A.P. Krymov, N.I. Kukudzhanov, Toskin-Zhebrovsky, Nyhus, Gilbert, Rutkow / Robbins, Schumpelick, Harkins, Casten, Halverson-McVay, Lichtenstein, Bendavid, Stoppa, Zollinger and the traditional (direct, indirect) – are the most widely-used classifications.

In 2009 the European Hernia Society (EHS) has adopted the following classification (tab. 1) [1]:

Table1

Classification of Inguinal Hernia
(European Hernia Society, 2009)

EHS Groin Hernia Primary / recurrent Classification					
	0	1	2	3	X
Lateral (indirect), L					
Medial (direct), M					
Femoral, F					

0 = no hernia detectable
1 = hernia < 1,5 cm (one finger)
2 = hernia < 3,0 cm (two fingers)
3 = hernia > 3,0 cm (more than two fingers)
X = not investigated

DIAGNOSIS

Typically, an inguinal hernia is detected during the original physical examination, the sensitivity of which is about 74, 5-92 % and specificity is up to 93 % [1, 4].

Diagnostic difficulties may arise in case when there is an indistinct boundary of hernial protrusion in the groin, which can periodically appear and disappear.

In some patients a hernial protrusion may not be palpable during the examination.

More rarely there are unspecific «inguinal» complaints against the backdrop of protrusion absence. Hernia with clear clinical implications does not require any additional examination. It is necessary to make the differentiation with femoral hernia, as it affects the surgical approach. Femoral hernia is situated below the inguinal ligament. Differential diagnostics between the direct or indirect hernia is not possible and is determined only intraoperatively.

Ultrasonography is a useful method that complements the physical examination.

In the diagnosis of hidden inguinal hernias the specificity of the method is about 88-100 %, sensitivity is 33-100 % [1]. Computer tomography doesn't play an important role in the inguinal hernia diagnosis. The sensitivity of the method is about 83 % and specificity is 67-83 % [5]. The method is useful when hernia contained urinary bladder.

The advantage of nuclear magnetic resonance imaging is the ability to identify comorbidities (inflammatory lesions, tumors). This method can be used to make hernia's dynamic estimates on activity. The sensitivity of the method is up to 94, 5 %, the specificity is 96, 3 % [5].

Herniography is a safe diagnostic aid of hidden hernias, the sensitivity of the method is up to 100 % and specificity is about 98-100 % [1]. This method is rarely used in domestic practice, although in foreign countries it is widespread. Herniography is performed by injecting a radiopaque substance into the abdominal cavity with a further study of its distribution by sloping areas during the fluoroscopy.

Herniography does not allow identifying a spermatic cord's lipoma, which can comes out in a pain syndrome and indistinct protrusion in the groin.

Inguinal hernias that have not been earlier accompanied by the protrusion were diagnosed in 12-54 % of patients undergoing herniography.

This method made it possible to detect hidden hernias in 25 % of athletes who have a vague pain in the groin area. The risk of complications of this method is about 0-4,3 %, which include allergy to the contrast substance, enterobrosia and abdominal wall hematoma [1, 3, 5].

If there is a vague pain in the groin area, unspecified diagnosis of inguinal hernia and the absence of negative trend, herniography should be done in no event sooner than 4 months after the specified symptoms' emer-gence.

A wide range of diagnostic techniques allows carrying out differential diagnostics of inguinal hernia to other diseases with a high reliability degree (tab. 2) [1, 5-6].

Table 2

Differential diagnosis of oligosymptomatic inguinal hernia

Differential diagnosis of inguinal hernia with other lumps in the groin and scrotum	**Differential diagnosis of inguinal hernia with diseases accompanied by the pain syndrome and groin protrusion absence**
Femoral hernia	Adductor tendinitis
Incisional hernia	Periostitis of the pubic symphysis
Lymph node swelling	Coxarthrosis
Saphena varix	Iliopectineal bursitis
Soft tissue tumors, including elements of the spermatic cord, epididymis and testis	Pain radiation of the lower spines
Abscess	Endometriosis
Genital malformations (ectopic testis, etc.)	
Hydrocele	
Endometriosis	

TREATMENT

The goal of the inguinal hernia's treatment is a symptoms reduction by removing hernia with minimal discomfort to the patient together with economic efficiency.

The treatment principle is the elimination of the posterior wall's defect of the inguinal canal. A support function of the transverse fascia of the Fruchaud's myopectineal orifice can be repaired through the autoplastic methods, either with the help of synthetic implant. Surgical treatment is required for all patients with the acute symptomatology of inguinal hernia.

The updated version of the EHS guidelines 2014 states that in case when men have a minimal symptomatology or have no hernia symptoms at all, then the expectant management is recommended. There indicated that over time with a probability of 70 % the symptomatology will increase, that in the result will inevitably lead to a surgical treatment [2].

Autoplasty

The most common surgeries are: hernioplasty by Kimbarovskiy, Kukudzhanov (the first and second methods) Spasokukotsky, Bassini, Girard, MacVay, Postemski and Shouldice [3]. According to domestic authors the anterior wall's repair of the inguinal canal is characterized by a high relapse rate - (9-37) % [1-2, 5]. This method does not apply in Western Europe and North America because it is not considered to be pathogenetically reasoned. The only indication to the anterior wall's plastic repair is an inguinal hernia in children – methods of Martynov and Roux-Krasnobaeva.

Shouldice's hernioplasty and in some cases Mac Vey's and Postemski's are the most preferable methods in foreign clinics and domestic herniological centers/ offices of autoplastic methods.

In 1884 Bassini described the first rational surgery to strengthen the posterior wall of the inguinal canal. The interpretation of this surgery was so arbitrary that there was not paid enough attention to a plastic repair of the transverse fascia. Consequently, the relapse rate reached a high level of 15 %.

In the 1950s Shouldice introduced a modern version of the original Bassini's technique, according to which the posterior wall of the inguinal canal and the internal inguinal ring are recovered by stitching of several layers with the help of long nonabsorbable monofilament suture. The Shouldice operation is considered to be the best among autoplastic techniques in the treatment of primary inguinal hernia according to recent recommendations of the EHS (2009) based on the metaanalysis [1-2, 5, 7]. In specialized herniological centers and branches the relapse rate of this operation is at a low level of 0,7-1,7 %. In general surgical departments the health outcome is slightly worse - the relapse rate reached a level of 15 % [8-9].

The shouldice repair technique

According to the technique it is necessary to make the incision in the ilio-inguinal area and secure subcutaneous veins. The aponeurosis of the transversus abdominis is incised while the ilio-inguinal nerve is preserved. The spermatic cord is isolated and taken to the ligature holder. Muscles of the spermatic cord are transected and secured.

If it is necessary there should be performed a transection and deligation of the spermatic cord's extrinsic vessels while a genital branch of genitofemoral nerve is preserved. Then a hernial sac is incised up to the internal inguinal ring and excised.

After that the transverse fascia is incised up to its unalterable areas. Reconstruction is performed by a continuous stitching using a 2,0 or 3,0 EP (European Pharmacopoeia Dimension) polypropylene suture. The first layer begins medially without trapping the pubic tubercle's periosteum. A lower edge of the transverse fascia (Thompson's ligament) is sutured to the upper flap which includes an anterior part of conjoined tendon. The layer is completed with the narrowing of internal inguinal ring. During the second layer it is used the same suture. A stump of cremasteric muscles with the superior flap of transverse fascia is trapped to the raphe from top, and a lower edge of the inguinal ligament (the ilio-pubic tract) - from below. The third layer begins laterally trapping the conjoined tendon from top and the inguinal ligament - from below. According to the original Shouldice's technique the fourth layer is stitched in the opposite direction. The aponeurosis of the transversus abdominis is sutured with the help of absorbable suture while the external inguinal ring should not be inordinately constricted. The Scarpa's fascia is blended and stitches are put in skin.

Hernia repair using mesh implants

A tension between tissues appears in the result of tissues' approximation, which under

normal conditions does not adjoin to each other. All classical autoplastic methods of hernioplasty according to which tissues are connected by stitches belong to the so-called «tension techniques». The tension of tissues leads to ischemia, enhancing pain syndrome, necrosis, disruption and hernia recurrence. Moreover, it is proved that some patients with inguinal hernia (especially elderly people) have an abnormality of collagen metabolism that also interrupts the scar's quality elaboration. Strengthening these tissues with synthetic material led to the creation of a new effective method.

The formation of the concept of «Tension-Free Hernioplasty» refers to the end of XIX century. Application of implants for the hernia's defects correction was termed - alloplasty.

By 1960s there has been created a polypropylene mesh that has met all the requirements applicable to the implants. Today, the monopolypropylene and composite mesh implants are the most commonly used. Defect's closure of the posterior wall of the inguinal canal by the implant can be done in two fundamentally different ways. According to the first method it is proposed to be used a tube implant, the second - a mesh implant in a form of a flap covering the transversalis fascia.

Implant insertion in the groin area can be performed anteriorly, through the inguinal incision and posteriorly - through the traditional inguinal access with its placement in the preperitoneal space, or endoscopically.

Selecting the mesh implant

For inguinal hernia's surgical treatment by the method of Tension-Free Hernioplasty it is recommended to use only non-absorbable mesh implants or composite meshes of non-absorbable materials.

There are a large number of mesh implants that differ in textile parameters such as the type of polymer, fiber, structure, pore size, elas-ticity, tensile and tear strength, weight and surface property.

Using mesh implants may be associated with the occurrence of non-specific (pain, in-fection, regression) and specific compli-cations (implant shrinkage, displacement, migration, damage of surroun-ding tissues and organs).

There are two most commonly used types of mesh implants - the heavy-weight meshes with small pore sizes and the light-weight meshes, characterized by a lower weight and a large «effective» pore (> 1000 μm).

Light-weight mesh implants do not actively shrink and they cause a less tissue inflammatory response, as well the formation of scar tissue is less. As a whole they cause less discomfort and initiate a less pronounced foreign body reaction.

The main disadvantage of light-weight mesh implants is a slight increase in the number of relapses. More often it happens in the result of malpositioning and wrong mesh fixing during large direct hernias.

Implantation through the open anterior approach

Since 1984 Lichtenstein actively promoted the method of Tension-Free Hernioplasty.

According to the technique it is necessary to make the incision in the inguinal area and it should be made so that it would be enough for a good visuality of pubic tubercle and sheath of rectus abdominis muscles, subcutaneous veins are to be secured. The aponeurosis of the abdominal external oblique muscle is incised while the ilio-inguinal nerve is preserved. The spermatic cord is isolated and taken to the ligature holder, while the posterior wall of the inguinal canal is exposed. Spermatic cord muscles are excised only in case of hypertrophy which causes an unacceptably large diameter of the internal inguinal ring. Hernial sac is isolated up to the internal inguinal ring and then it can be opened, excised or invaginated. If, in the case of direct hernia, the transverse fascia is significantly stretched, it is necessary to put a continuous suture with the help of absorbable suture, which will constrict the internal inguinal ring to its normal size. During the operation all the groin nerves are preserved. A special attention is paid to the ilio-hypogastric nerve, which can be placed directly under the mesh implant, but only not under its sharp corner, which may lead to a persistent postoperative neuralgia. Thus, it is necessary to cut out the mesh flap of sufficient size. For a Lichtenstein hernioplasty is used a 7×14 cm piece of polypropylene mesh implant covering the pubic tubercle by 2 cm. Fixation is performed by a 3,0 EP (European Pharmacopoeia Dimension) polypropylene suture, 2 cm medial to the pubic tubercle, starting from the lateral border of the rectus sheath with the transition to the inguinal ligament and up to the internal inguinal ring.

Next, a lateral one third of the mesh is medially excised along the spermatic cord. The 2 tails are then tucked together, sutured and fixed to the inguinal ligament. The upper edge of the mesh implant is sutured by interrupted or continuous stitches to the aponeurosis of the internal oblique abdominis. It is important to avoid the entrapment of the internal oblique muscle taking into account that the ilio-hypogastric nerve may be injured. According to the first randomized trial the usage of cyanoacrylate for the polypropylene mesh fixing can be accompanied by the pain reduction in the postoperative period (a level of evidence 1B). However, there were no advantages over the sutural technique with regard to chronic pain. According to the recommendations of the B level, an atraumatic mesh fixation can be performed without the first-year relapse rate increasing [2, 10].

After the implantation the mesh should be like a small dome, indicating the tension absence. In other words, the mesh is implanted with a small overlap. Then the flaps of the aponeurosis of the external oblique abdominis are sutured edge-to-edge over the spermatic cord.

As for inguinal hernia repair in women it should be a very careful attitude to the round ligament and ilio-inguinal nerve, in men – to the spermatic cord. If during the operation the anatomical structures intersected, the lateral part of the mesh implant is not to be incised.

Besides Lichtenstein method there are the following most commonly used types of implants and the ways of their anterior approachable positioning:

- mesh-plugs (a plug is located in the internal inguinal ring and an implant's mesh part covers the posterior wall of the inguinal canal),
- PHS (Polypropylene hernia system) – the implant, covering three areas – the preperitoneal space, deep inguinal ring and posterior wall of the inguinal canal,
- Trabucco performs a sutureless implantation of the mesh,
- Rives performs a preperitoneal mesh-implantation through the inguinal approach.

Implantation through the open posterior approach

Posterior approach to the Fruchaud's myopectineal orifice is performed by discission of the abdominal wall. A large implant that completely covers all the orifices of this area is set into the preperitoneal space through the discission. The method was popularized in the 1980s by Stoppa. First surgeons who advanced this idea were Goss, 1962 and Mahorner, 1962. Stoppa and Wantz applied this method for the unilateral inguinal hernias treatment. Today Stoppa's operation remains the method of choice for the recurrent and bilateral inguinal hernia treatment. Kugel offered to put a mesh implant with a solid outer ring into the preperitoneal space. During short-term observations this method shows the results comparable to Liechtenstein's operation.

Inguinal hernia in females

About 8-9 % of all inguinal and femoral hernia operations are performed to women [1]. Women undergoing autoplastic method of hernia repair have a comparable number of relapses (2-13%) with similar operations of oblique and direct inguinal hernia conducted in men [1]. At the same time a relapse rate depends on the postoperative term. According to epidemiological studies of different countries, the frequency of reoperation in women is slightly higher than men have, and it does not depend on the type of hernia repair – allo-or autoplastic. A recurrence of femoral hernia is detected during the operation in about 40% of the cases. There is a pending issue whether these "femoral" recurrences are occult hernias during the previous operation or they formed de novo [1, 9]. Endoscopic plastic according to which the mesh implant simultaneously closes both orifices (inguinal and femoral) is justified by a high relapse rate of femoral hernias in women after the inguinal hernia repair.

Indirect inguinal hernia in young males

Taking into account possible recurrences of inguinal hernia and the negative impact of repeated operations, as well as the impact of mesh implant on fertile function, experts of the EHS was carried out a deep analysis of treatment results in this group of patients. Approximately 5 % of all inguinal hernia repairs are performed to men at the age of 18 - 30 years. Indirect inguinal hernia is the most widespread in the majority of cases. Moreover, during the period from 2 to 5 years after Shouldice hernioplasty the number of relapses during indirect inguinal hernia is 1-3 % lower than the number during the direct [1, 2].

During Danish Hernia Database analyzing there were detected that in men younger than 30 years with primary indirect inguinal hernia

after the autoplastic hernioplasty the frequency of repeated operations almost twice higher in comparison with the Liechtenstein's operation and other open methods of alloplasty [2]. At the same time, in patients under 55 years, who were operated for indirect inguinal hernia by both auto-and alloplastic methods, there was no significant difference in the incidence of chronic pain and the occurrence of specific complications in the case of mesh implantation. Currently, there are no data indicating an advantage of autoplastic hernia repair in young men in comparison with alloplasty. EHS recommends using mesh implants in men at the age of 18-30 years, regardless of inguinal hernia type [3].

Antibiotic prophylaxis

Routine antibiotic prophylaxis is not recommended during the scheduled inguinal hernia repair in patients with a low risk of wound complications (level A). Antibiotic prophylaxis is considered mandatory in establishments with a high risk of wound infection (more than 5 %). Standard agents are the second-generation cephalosporins.

Debatable questions

The most mandatory method of open inguinal hernia repair

The following factors should considered while choosing a treatment method of inguinal hernia: the risk of recurrence, the risk of complications (safety), the patient restoration in the postoperative period, the quality of life, terms of return to work, the degree of complexity, and cost.

According to systematic reviews, meta-analyzes and individual studies published in reliable publications, the operations of choice are as follows [7-19].

- For the primary inguinal hernia treatment, among the methods that do not use mesh implants, Shouldice hernioplasty is the operation of choice, which gives no more than 1.7 % of relapses in specialized centers and offices
- Liechtenstein hernioplasty is the operation of choice among the methods with the mesh implant open offering. Operation is characterized by a low rate of postoperative mortality, it may be performed in the one-day surgical hospital and during long observation relapse rates does not exceed 4 %

What to choose: autoplasty or a mesh?

According to systematic reviews of randomized controlled trials the relapse rate is less while using mesh implants than while performing autohernioplastic interventions, especially Shouldice's operation [5, 10-11, 20-32].

A mesh implants application is characterized by reducing risk of chronic pain. On the other hand, many authors notes that the statistical advantages of the mesh implants usage are associated with technical errors of Shouldice's operation.

Prospects for treatment

In the last 5-7 years there appears more data pointing the benefits of laparoendoscopic hernioplasty (TAPP and TEP) [2, 5, 33-34]. It is necessary to notice that there are a reduction of the frequency and intensity of pain syndrome in the early postoperative period and wound complications abatement. A bed day is less and there is a short period of rehabilitation. Relapse rate is comparable with open methods.

If there is a hernia recurrence after open surgery, laparoendoscopic hernioplasty offers the possibility to reduce postoperative pain syndrome, speed a recovery and reduce the risk of chronic pain compared with Liechtenstein's operation (a level of evidence 1A) [2].

Transabdominal preperitoneal hernioplasty (TAPP) is widespread in large surgical centers of Western Europe, totally extraperitoneal hernioplasty (TEP) – in the United States [2, 3,16]. The main disadvantage of laparoendoscopic hernioplasty is a high cost due to the price of endoscopic rack, instruments, and anaesthetic support. Another deterrent on the way toward a wider implementation of these operations is a surgery technique complexity, especially of extraperitoneal hernioplasty (TEP) on the background of the lack of simulation training centers [29-34].

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THE MAIN PRINCIPLES OF INSULIN THERAPY

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The article describes the main indications for insulin therapy, insulin agents and their characteristics depending on the origin, methods of producing and action duration. The article elucidates the methods of insulin injection and injection technique. Also, this article presents the insulin therapy regimen: the conventional and basal-bolus therapy, the daily insulin demand depending on the DM period and its distribution throughout a day. Besides, the article deals with the morning hyperglycemia syndromes, their differential diagnostics and therapeutic approach.

KEY WORDS: diabetes mellitus type 1, insulin, Standard Medical therapy, basal-bolus therapy, insulin therapy regimen

ЗАГАЛЬНІ ПРИНЦИПИ ІНСУЛІНОТЕРАПІЇ

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У статті представлені основні показання до призначення інсулінотерапії, препарати інсуліна та їх характеристики залежно від походження, методу отримання і тривалості дії. Висвітлено питання способу введення інсуліну та техніки виконання ін'єкції. Описано режими інсулінотерапії: традиційна і базисно - болюсна, визначення добової потреби в інсуліні в залежності від періоду перебігу цукрового діабету та його розподіл протягом дня. Розглянуто синдроми ранкової гіперглікемії, їх диференційна діагностика та тактика лікування.

КЛЮЧОВІ СЛОВА: цукровий діабет 1 типу, інсулін, стандартна терапія, базисно-болюсна терапія, режими інсулінотерапії

ОСНОВНЫЕ ПРИНЦИПЫ ИНСУЛИНОТЕРАПИИ

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В статье представлены основные показания к назначению инсулинотерапии, препараты инсулина и их характеристики в зависимости от происхождения, метода получения и длительности действия. Освещены вопросы способа введения инсулина и техники выполнения инъекции. Описаны режимы инсулинотерапии: традиционная и базисно-болюсная, определение суточной потребности в инсулине в зависимости от периода течения сахарного диабета и его распределение в течение дня. Рассмотрены синдромы утренней гипергликемии, их дифференциальная диагностика и тактика лечения.

КЛЮЧЕВЫЕ СЛОВА: сахарный диабет 1 типа, инсулин, стандартная терапия, базисно-болюсная терапия, режимы инсулинотерапии

INSULIN THERAPY

100 % of patients with diabetes mellitus (DM) type 1 (DM-1) need insulin therapy, as hyperglycemia that was caused by absolute insulin deficit can be negated only with the help of replacement therapy institution. A diet and physical activity are considered only for insulin dose modification [1, 2].

Besides, up to 40 % of patients with DM type 2 (DM-2) are on the insulin [2, 3].

GENERAL INDICATIONS FOR INSULIN THERAPY [1-3]

1. DM-1.
2. DM-2, in such cases:
   - progressive weight loss and ketoacidosis expansion;
   - surgical intensive interference;

- acute macrovascular complications;
- serious virulent diseases;
- glycemia's level is more than 15-18 mmol/L;
- permanent lack of compensation in case of maximum daily dose administration of tableted antihyperglycemic drugs;
- advanced stages of the DM's chronic complications.

3. Ketoacidotic and hyperosmolar coma.
4. Gestational DM without compensation achievement.
5. Pancreatectomy.

INSULIN AGENTS' CLASSIFICATION

Insulin agents are divided by origin and action duration [3,4].

I. By origin:

1. Of animal origin:
   a) Porcine,
   b) Beef;
2. Of human origin:
   a) Genetically engineered,
   b) Semisynthetic;
3. Insulin human analogues - with fixed pharmacokinetics.

Porcine insulin is distinguished from human origin insulin by one amino acid and the beef one - by three amino acids, that leads to its greater antigenic specificity. Recently animal origin insulins are rarely used. There are two methods of producing human insulin: a semi-synthetic (with the help of porcine insulin, by replacing one differ amino acid), and genetically engineered.

Genetically engineered human insulins are of the highest quality, as they are produced by the association of human genome's locus, responsible for insulin release ,with the yeast cultures genome or E.coli, that start to produce human insulin.

Genetically engineered insulins - are agents of choice in the course of the DM-1 treatment (especially for the youngsters under the age of eighteen) [4, 5].

Insulin analogues were obtained in the result of the amino acids' misplacement in order to get fixed pharmakokinetics agents (of ultrashort and long-act).

Insulin analogues are recommended in cases of intolerance to other types of insulin and during the labile DM with a tendency to severe hypoglycemia.

If the compensation of DM was achieved, it isn't recommended to switch to other insulin types [3].

II. By action duration:

1. Ultrashort-acting (insulin human analogues);
2. Short-acting (regular insulin);
3. Intermediate-acting (Neutral Protamine Hagedorn);
4. Long-acting (insulin human analogues).

Table 1 describes the characteristics of insulin agents.

Table 1

Insulin agents'characteristics

Insulin types	**International nonproprietary name**	**Effect**		
		Onset	Peaktime	Duration
Ultrashort-acting	Insulin lispro Insulin aspart Insulin glulisine	5-15 min	1-2 h	4-5 h
Short-acting	Soluble genetically engineered human insulin	20-30 min	2-4 h	5-6 h
Intermediate-acting	Isophane genetically engineered human insulin	2 h	6-10 h	12-16 h
Long-acting	Insulin glargine Insulin detemir	1-2 h	-	Up to 24 h

Ultrashort-acting agent should be injected immediately preprandial, short-acting - a 30 minute before meals. A short duration effect of ultrashort acting insulin reduces the hypoglycemia risk [6]. Ultrashort- and short-acting agents can be injected in a subdermic, intramusculary and endovenous way [3-7].

Among the intermediate-acting insulin the most popular agents are those that include Neutral Protamine Hagedorn (NPH), which adsorbates insulin noncovalently, reducing its subcutaneous fat absorption [3].

NPH doesn't bind insulin's additional amounts and as a result it is possible to create standard mixtures with short-acting insulin (diphasic genetically engineered human insulin) and ultrashort insulin analogues (diphasic insulin lispro and aspart) [7]. It is possible to combine short- and ultrashort-acting insulins with protamined insulin in different proportions such as 25/75, 30/70 or 50/50. Usually only the first digit is on the product name and it indicates the percentage of regular insulin, the second one - attends to NPH insulin.

The advantage of insulin's standard mixtures is a substitution of two injections for one, the downside - inability to separate the individual dosing components out of the mixture [3, 7].

Long-acting insulin analogues provide more uniform and prolonged agent's admission from subdermal repository, than NPH insulin, that can be injected once a day, regardless of the time of day. [8].

THE INJECTION TECHNIQUE

In general the success of insulin therapy depends on strict implementation of injection technique.

The simplest and the most reliable method is insulin injection using an insulin syringe. The method of insulin injection using an automatic syringe device, which consists of the insulin cartridge, dose delivery system and skin wheal needle with the pressure infusor, is more convenient for patients. For maintenance therapy insulin should be administered subcutaneously: short-acting insulin - to the subcutaneous fat of the abdomen, prolonged - to the pacefollower of the shoulder or hip. The needle is to be located at an angle of 45° to the skin fold, if the thickness of subcutaneous fat layer exceeds the length of the needle - of 90°. At the same time, in order to prevent lipodystrophy, the injection site within the same zone should be daily changed [3-5, 9].

Daily-used insulin vials or injection pens can be stored at indoor temperature during one month; insulin is to be of indoor temperature before being injected. Intermediate-acting insulins (NPH insulins) and ready-made insulin mixtures should be mixed meticulously before the injection [9].

The insulin pump usage is one of the insulin injection methods. It allows to make the basal insulin injection at the rate of 0.5-1.0 U/h with the additional insulin injection before meals, depending on the consumed carbohydrate and glycemia [3, 7]. The positive aspect of insulin pump usage is the ability to inject only short-acting or ultrashort-acting insulin. It is more physiological, because prolonged insulin absorption is exposed to large fluctuations [10]. The disadvantages of insulin pump injection are: inconvenience caused by constant wearing of a device on the body and long-term presence of the injection needle in the subcutaneous tissue. The indications for insulin pump usage are: decompensated or refractory DM, the dawn phenomenon patients, pregnant or planning pregnancy women with DM-1 [9, 10].

INSULIN THERAPY REGIMEN

In arriving at a DM-1 diagnosis, short-acting insulin is prescribed subcutaneously 4-6 times a day before meals. A few days later it is necessary to start the combined insulin injection. The average daily insulin demand in patients with DM-1 is 40 - 60 units.

In early disease the required amount of insulin is 0.5-0.6 U/kg.

After insulin therapy initiation the insulin requirement may even decrease (0.3-0.4 U/kg) - the «honeymoon period». This period can last from several weeks to several years (on average for several months), but the autoimmune destruction of the rest of endocrine pancreas will inevitably lead to increasing insulin requirement up to 0.7-0.8 U/kg [3, 4].

The DM-1 decompensation will lead to even greater insulin demand - 1.0-1.5 U/kg [3, 4].

Insulin therapy must be individualized in order to achieve the best control of DM progression in the setting of the absence of severe hypoglycemia.

Normally the pancreatic secretes 35-50 units of (0.6-1.2 U per 1 kg body mass) insulin per day. This secretion is divided into *nutritional* or *bolus* (50-70 % of daily output) and *basal*.

The neutralization of postprandial hyperglycemia occurs at the expense of food insulin secretion - about 1-2.5 U per 10-12 g of carbohydrates (= 1 bread unit -BU). 2.0-2.5 units of insulin are secreted at 1 BU during breakfast, 1.0-1.5 units at lunch and 1.0 unit at diner. It is connected with the greatest activity of counter-insulin hormones in the morning [3, 4].

Basal insulin secretion (with a rate of 1 U/h) provides an optimal level of glycemia between meals and during a sleep.

The conventional insulin therapy involves the usage of standard mixtures with a fixed dose of insulin, which is more preferable for patients with DM- 2 [3, 4, 7].

Intensive insulin therapy with flexible choice of the dose which depends on glycemia and on the amount of carbohydrates in food is more approximated to a physiological insulin secretion [11]. The need for basal insulin secretion is provided by two intermediate-acting insulin injections (⅔ in the morning and ⅓ in the evening) or a single injection of long-acting insulin (does not matter in what time of day). A daily dose of basal insulin should not be more than a half of agent's total daily requirement (⅓ - ½). *Food insulin secretion* is replaced by short-acting or ultra short-acting insulin before each meal (¼ at dinner, the remaining dose is divided roughly in two parts between breakfast and lunch), taking into account the amount of carbohydrates which the patient is going to take during the meal. Not all carbohydrates are taken into account, but only «carb counting», such as: fruits, potatoes, grains, sweet and liquid milk products. You can count a matching insulin dose with the help of special exchange tables that were developed for the patients' convenience (tab. 2). For each BU, that is planned to be eaten, 2 U of insulin should be injected in the morning, 1,5 U at lunch and 1U at dinner [3, 4, 7].

Table 2

The exchange table of products containing 1 BU

Product description	Portion size	Dimension
Milk, kefir, curdled milk, whey	1 cup	250 ml
Cheesecake (medium-sized)	1	75 g
Ice-cream	⅔ of portion	65 g
Boiled groats (porridge)	2 tablespoons	50 g
Vermicelli, noodles, elbows	1,5 tablespoons	
Bread, small loaves except buns	1	25-30 g
Pancakes with cheese	1	
Sand sugar	1 tablespoon	12 g
Refined sugar	2-2,5 pcs	12 g
Mashed potatoes	1-1,5 tablespoons	
Fried potatoes	1,5-2 tablespoons	
Carrot (large)	3	
Kidney bean	7 tablespoons	120 g
Beetroot (large)	1	
Banana (with peel weight)	0,5	90 g
Pear	1	90–100g
Melon		300 g
Watermelon		400 g
Peach (medium-sized)	1	120 g
Apricots, blue plums (medium-sized)	3	120 g
Mandarines, oranges	1	170 g
Apples(medium-sized)	1	100-120 g
Strawberries (medium-sized)	10	120 g
Cherry (large)	15	120 g
Strawberries, blackberries, raspberries, black currants, gooseberries, cranberries	1 cup	100 g
Apple juice, grapefruit and orange juice	0,5 cup	100 g
Dumplings	4 pcs	
Cooked sausage, sausages		100 g
Cutlet (medium-sized)	1	

A short-acting and long-acting insulin doze depends on the amount of eaten carbohydrates (BU) and glucose level before the injection. While meal, containing 1 BU increases glycemia at 1.6-2.2 mmol/L, the injection of insulin (1U) reduces it to the same level. Short-acting insulin is injected with morning dose of NPH insulin. Evening dose of NPH insulin is prescribed for 22-23 hours. It is necessary to consider the probability of typical phenomena development during the selection of evening intermediate-acting insulin dose.

The *dawn phenomenon* is morning hyperglycemia associated with the lack of evening prolonged insulin dose, in the setting of increasing morning insulin requirement [3, 4, 12, 13].

The *Somogyi effect* also occurs through morning hyperglycemia and develops after the precursory hypoglycemia. The excessive evening dose of prolonged insulin leads to night hypoglycemia (between 2:00 and 4:00 a.m.), when the counter-insular hormones level is minimal and tissues are the most sensitive to insulin. During this period hypoglycemia stimulates the compensatory release of counter-insular hormones (including glucagon) that leads to morning hyperglycemia. Clinically nocturnal hypoglycemia manifests as a poor sleep with nightmares, sweating, morning weakness and a headache. Choosing insulin therapy, glucose testing should be carried out at 3am in order to get proper diagnosis of morning hyperglycemia (the dawn phenomenon or the Somogyi effect) [3, 13].

The common rules of insulin therapy are [4]:

1. The regular insulin dose should not exceed 12 units in a single injection.
2. The total dose of a combined injection should not exceed 70-80 units.
3. The ratio of a daily and nightly insulin dose should be about 2:1.
4. The daily insulin dose cannot be changed more than 4 U/day.
5. Simultaneously a daily insulin dose should not be increased or decreased by more than 6-8 units.

And as conclusion I would like to quote the words of a German doctor Michel Berger: «Diabetes is not a disease but a way of life. Sick with diabetes – all the same that drive the car on a busy road – be aware traffic rules».

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Lecture

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CLINICAL PHARMACOLOGY OF DIURETICS

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Clinical pharmacology of diuretics in the international system of ATC (anatomic-therapeutic-chemical) is presented. Classification of this group by the action mechanism and caused effects is provided. Pharmacokinetics and pharmacodynamics features, indications and principles of diuretics usage in clinics are considered. Contraindications, side effects and interaction with other drugs of this group are discussed in detail.

KEY WORDS: clinical pharmacology, diuretics

КЛІНІЧНА ФАРМАКОЛОГІЯ СЕЧОГІННИХ ПРЕПАРАТІВ

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Висвітлена клінічна фармакологія сечогінних препаратів у рамках міжнародної системи класифікації лікарських засобів АТХ (анатомо-терапевтично-хімічної). Представлені класифікації даної групи препаратів за механізмом дії та надаваними ефектами. Розглянуті особливості фармакокінетики та фармакодинаміки, показання та принципи використання в терапевтичній клініці сечогінних препаратів. Детально висвітлені протипоказання, побічні ефекти і взаємодія з іншими лікарськими засобами препаратів даної групи.

КЛЮЧОВІ СЛОВА: клінічна фармакологія, сечогінні препарати

КЛИНИЧЕСКАЯ ФАРМАКОЛОГИЯ МОЧЕГОННЫХ ПРЕПАРАТОВ

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Освещена клиническая фармакология мочегонных препаратов в рамках международной системы классификации лекарственных средств АТХ (анатомо-терапевтическо-химической). Представлены классификации данной группы препаратов по механизму действия и оказываемым эффектам. Рассмотрены особенности фармакокинетики и фармакодинамики, показания и принципы использования в терапевтической клинике мочегонных препаратов. Подробно освещены противопоказания, побочные эффекты и взаимодействие с другими лекарственными средствами препаратов данной группы.

КЛЮЧЕВЫЕ СЛОВА: клиническая фармакология, мочегонные препараты

INTRODUCTION

At present diuretics represent first line medications for arterial hypertension [1], hyperkalemia [2] and electrolyte disorders [3, 4] treatment.

As far back in the XVI century it was clear that organic mercury compounds have diuretic characteristics but as diuretics they have been used in medicine since 1920 in Vienna. The next stage in diuretics creation was based on the results of acidosis development observation in patients, who got sulfanilamides, which is not typical for modern sulfanilamide remedies. Acidosis was clarified to be stipulated for carbonic anhydrase enzyme inhibition in kidneys [5]. Further studies caused the creation of powerful inhibitor of acetazolamide carbonic anhydrase in 1951 [6]. In 1957 in the process of preparations chemically close to

acetazolamide study chlorothiazide was obtained, which weakly inhibited carbonic anhydrase, that is why this property could not explain their diuretic efficacy [7]. Both acetazolamide and thiazide structurally are close to sulfanilamides. Their structure modification caused the creation of more effective diuretics, such as furosemide, etacryn acid, bumetanide as well as potassium preserving diuretics such as triamteren and amiloride, etc. [8].

CLASSIFICATION OF DIURETICS

ATC classification

C: MEDICATIONS, EFFECTING CARDIO-VASCULAR SYSTEM
C03 Diuretics
C03A Diuretics with moderately expressed activity, thiazides group
C03AA Simple thiazide diuretics
C03AA03 Hydrochlorothiazide
C03B Nonthiazide diuretics with moderately expressed activity
C03BA Sulfanilamides, simple preparations
C03BA03 Clopamide
C03BA04 Chlorthalidone
C03BA11 Indapamide
C03BX Other nonthiazide diuretics with moderately expressed effect
C03BX10 Herbal preparations with diuretic effect
C03C Highly active diuretics
C03CA Simple sulfamides preparations
C03CA01 Furosemide
C03CA02 Bumetanide
C03CA04 Thorasemide
C03C3 Derivatives of aryloxyazinyl acid
C03CC01 Etacrin acid
C03D Potassium preserving diuretics
C03DA Aldosterone antagonists
C03DA01 Spironolactone

Classification depending on the scene of action in nephron

Classification of diuretics depending on their scene of action in nephron is widely disseminated in clinical practice:

1) on proximal part of straight tubule:

a) Carbonic anhydraze inhibitors (acetazolamide).

b) Osmotic diuretics (mannitol, urea).

2) on ascending area of Genle loop - «loop» diuretics (furosemide, etacrin acid, etc.);

3) on distal part of straight tubule – thiazide and thiazide-like diuretics (hydrochlorothiazide, chlorthalidone, indapamide, etc.);

4) in general in the area of collective and distal tubules (potassium preserving diuretics);

5) onglomerule (aminophylline, teobromine).

Classification depending on natriuretic effect

Diuretics are divided into the groups depending on natriuretic effect, expressed in percentage of excelling sodium from general amount of sodium, filtered in renal tubules:

1) strong organic compounds of mercury (mersalile, at present it is not used in clinical practice):

– derivatives of sulfamonlantranile acid (furosemide, bumetanid);

– derivatives of phenoxy-acetic acid (etacrin acid, indacrinon).

2) With moderately expressed natriuretic effect (causing excretion of 5-10 % sodium, filtered):

– derivatives of bensotiathiazine (thiazides and hydrothiazides).

– heterocyclic combinations similar in mechanism of tubule activity to thiazide diuretics (chlorthalione, clopamide, indapamide).

3) weak (causing excretion of less than 5 % filtered sodium):

– potassium preserving;
– carbonic anhydraze inhibitors;
– osmotic diuretics.

PHARMACOKINETICS

Main pharmacokinetic indicators of diuretics are presented in table 1.

Loop diuretics nearly completely absorb from gastrointestinal tract, though absorption individual indices vary greatly. They relatively quickly metabolize in liver.

Thiazides and thiazide-like diuretics have high bioavailability under intake. Due to sufficient lipophilicity and moderately expressed link with proteins they deeply penetrate into organs and tissues. Hydrochlorothiazide and chlorthalidone poorly metabolize in liver and is nearly absolutely excreted by kidneys unchanged. Indapamide practically completely metabolize in liver and only a tiny part of active remedy is excreted by kidneys.

Carbonic anhydrase inhibitors are practically completely absorbed from gastrointestinal

tract. In 95 % of cases they are linked with protein in blood plasma. They are mot metabolized in organism and are completely excreted by kidneys unchanged.

Table 1

Main pharmacokinetic indicators of diuretics

Diuretic	Bioavailability (%)	$T_{1/2}$ (h)	Main way of elimination
Thiazide diuretics:			
Hydrochlorothiazide	60-80	10-12 (2,5)	Kidneys
Indapamide	90-100	15-25	Kidneys + liver (30 %)
Clopamide	?	4-6	Kidneys
Xipamide	70-90	5-7 (14)	Kidneys + liver
Metolazone	50-60	8-14	Kidneys + liver
Chlorthalidone	60-65	24-50	Kidneys + liver
Chlorthiazide	33-65	15-27 (1,5)	Kidneys + liver
Loop diuretics:			
Bumetanide	60-90	0,3-1,5	Kidneys + liver
Pyretanide	80-90	0,6-1,5	Kidneys + liver
Torasemide	80-90	0,8-6,0	Kidneys + liver
Furosemide	10-90	0,3-3,4	Kidneys + liver (40 %)
Etacrin acid	30-35	12	Kidneys + liver
Potassium preserving diuretics:			
Amiloride	50	6-9 (18-22)	Kidneys + liver (50%)
Spironolactone	60-90	14 (1,5)	Kidneys + liver (20%)
Triamteren	50	3-5	Kidneys + liver

Note: $T_{1/2}$ – semi-ejection period; in brackets – other meanings of $T_{1/2}$, if they rapidly differ from the given/

Potassium preserving diuretics have variable absorption. Triamteren is linked with plasma proteins in 56 % of cases, it is relatively quickly metabolized by liver enzymes, forming active metabolite 4-hydeoxytriamteren sulphate, which is secreted into proximal area of kidney tubules opening with the help of active transport mechanism. Amiloride is weakly linked with plasma proteins, it is not metabolized in organism and is excreted into proximal area of kidneys tubules unchanged.

Aldosterone derivatives are slowly absorbed from gastrointestinal tract, just during the first transport through liver they are subjected to expressed biotransformation. In this case some metabolites are formed, two of which display the same pharmacological activity as spironolactone. The link of spironolactone with plasma proteins exceeds 90 %. It has a short period of semi-excretion (1,6 h), though the period of its active canrenon metabolite semiexcretion reaches 10-16 h, which lengthens spironolactone biological effect.

Both liver and renal failure lower diuretics clearance and can raise their toxicity.

PHARMACODYNAMICS

Pharmacodynamic effects of diuretics are hypotensive, antianginal, antiatherogenic, dehydrative and others.

Hypotensive effect of diuretics is connected with influence on one of the pathogenic mechanisms of arterial hypertension development – sodium latency in organism. Two possible main mechanisms of hypotensive activity are discussed: decrease of sodium content and, consequently, liquid volume in organism and effect on vessels regardless natriuresis. Thus antihypertensive effect can be stipulated for initial decrease of liquid volume in organism (first 3-4 weeks of therapy), and further (after 6-8 weeks) – protractedly supported decrease of vessels reaction on sympathy nervous stimulation (periphery vasodilatation), which can be of compensatory character in response to tiny but long term decrease of blood plasma volume.

Arterial pressure decrease is reached on account of both depletion of sodium chloride

reserves and vascular effects regardless natriuresis amount.

Antianginal effect of diuretics is stipulated for intracellular calcium decrease with magnesium content preservation, decrease of vascular wall stiffness and promote of effective cardiomyocytes relaxation into diastole. In this case prostacyclin synthesis increases, thrombocytes aggregation and thromboxane A2 ejection decreases, totally exerts positive hemodynamic effect on account of loading decrease on left ventricle. Diuretics improve microcirculation in kidneys, eliminate microalbuminuria which is the marker of generalized vascularaffection and a predictor of cardio-vascular and renal complications.

Antiatherogenic effect of diuretics (indapamide) is stipulated for decrease of low density atherogenic cholesterol and triglycerides level with simultaneous increase of high density lipoprotein concentration.

Dehydration effect of diuretics (mannit, urea) is stipulated for increase of osmotic pressure in tubules and water reabsorption obstruction. They are filtered by kidneys without further tubular reabsorption which causes water retention in tubules and increase of urine volume. Simultaneously natriuresis increases considerably without potassiumuresis sufficient increase. They cause increase of circulating liquid volume (in connection with osmotic pressure growth in bloodstream), decrease of intracranial and intraocular pressure. Oppression of carboanhydrase causes decrease of intraocular pressure, inhibition of excessive paroxysmal neurons discharges and antiepileptic activity.

Antiepileptic effect (acetozolamide) is stipulated for random suppression of carboanhydrase (enzyme, catalyzing reverse reaction of carbon dioxide hydratation and further carbonic acid dissociation).

According to LIVE trial (Left ventricular hypertrophy: Indapamide Versus Enalapril) on the background of long term indapamide therapy - 1,5 mg per day - reliable decrease of mass index of left ventricle was observed versus enalapril therapy (20 mg per day).

According to most experimental and clinical studied diuretics have no sufficient nephroprotective activity. On the contrary, their monotherapy can accelerate renal function decrease in spite of antihypertensive effect. Though the results of early trial HYVET (Hypertension in the Very Elderly Trial) in elderly patients demonstrated that indapamide produced nephroprotective activity.

Diuretics provide bronchodilatory and spasmolytic effects (aminophylline and teobromine) on the account of bronchial smooth muscles, periphery arteries, gastrointestinal smooth muscles, biliary tract relaxation. They also increase contractility of skeleton muscles (including respiratory).

INDICATIONS AND USAGE PRINCIPLES

Main indications to diuretics clinical use are:

– arterial hypertension (AH): isolated systole AH in elderly persons;

– edematous syndrome, cause by Na delay: chronic heart failure (CHF), chronic renal failure (CRF), nephritic syndrome, edemas and ascites under hepatocirrhosis;

– osteoporosis, hypercalcemia (thiazides);

– (primary) open angle glaucoma, secondary glaucoma, pre-operative decrease of intraocular pressure (carbonic anhydrase inhibitors);

– pseudohyperaldosteronism – Liddle syndrome (potassium preserving diuretics);

– primary and secondary hyperaldosteronism (spironolactone);

– hyperuricemia (spironolactone).

Daily doses and reception frequency of diuretics are presented in tab. 2.

SIDE EFFECTS

Most side effects of diuretics are connected with electrolytic and water balance changes, urine pH shift into alkaline side and metabolic acidosis development. Such side effects are:

Electrolytic: intracellular liquid reserves depletion, arterial hypotension, hypocalcaemia (thiazides), hyperkalemia (aldosterone antagonists, potassium preserving diuretics), nyponatremia, nypochloremia, metabolic alkalosis, hypomagnesaemia, hypocalcaemia, hyperuricemy.

Central nervous system (CNS) disorders: dizziness, headache, weakness, parasthesias.

Gastrointestinal: anorexia, nausea, vomiting, colic, diarrhea, constipation, cholecyctitis, pancreatitis.

Sexual: impotence, libido decrease.

Hematologic (blood dyscrasia): thrombocytepenia, agranulocytosis, thrombocytopenia purpura.

Dermatologic: skin rush, photosensibilization.

Other: hyperglycemia, increase of general cholesterol level in blood, triglycerides level increase, low density lipoproteins level increase.

Table 2

Daily doses and the reception frequency of diuretics

Diuretic	Average doses (mg/day)	Reception frequency	Note
Thiazides			
Hydrochlorotheozide	12,5-50	1	Most efficient for AH treatment than loop diuretics excluding the patients with creatinine more than 177 mcmole/l
Thiazide-like diuretics			
Chlorthalidone	12,5-25	1	
Indapamide-retard	1,5	1	
Loop diuretics			
Torasemide	2,5-10	1-2	The use of big doses is possible in treatment of patients with CRF and CHF.
Forisemide	20-80	1-2	
Potassium preserving diuretics			
Amiloride	5-10	1-2	Is not used if creatinine is more than 220 mcmole/l
Tiamteren	50-100	1-2	
Aldosteron antagonists			
Spironolactone	25-50	2-3	Is not used if creatinine is more than 220 mcmole/l

CONTRAINDICATIONS

Hypokalemia, gout, asymptomatic hyperuricemia, decompensated hepatocirrhosis, sulpha-nilamide derivatives intolerance (hypo-glycemic and antibacterial preparations), severe respiratory failure, acute renal failure. In high doses thiazide diuretics are contrain-dicated under sugar diabetes, especially of the 1st type. Diuretics should be prescribed with great care to the patients with ventricular arrhythmias or to those who get heart glycosides or lithium salts.

INTERCONNECTION OF DIURETICS WITH OTHER REMEDIES

Loop diuretics are able to interact pharmacodynamically and pharmacokinetically with many preparations.

They reinforce the activity of anticoagulants, hypotensive remedies, semipolarizing myorelaxants; raise the side effects development risk of aminoglycosides, heart glycosides and diuretics, excreting potassium and GCS; raise propranolol and lithium concentration in blood plasma; lower oral hypolipidemic remedies effects. Diuretics activity can decrease under simultaneous application together with indomethacin and other non-steroid anti-inflammatory drugs (NSAIDs).

Thiazide and thiazide-like diuretics lower the efficacy of antigout remedies, sulphonylurea preparations, insulin. They can reinforce the activity of anesthetics, diasoxide, heart glycosides, lithium preparations and loop diuretics.Such remedies as NSAIDs and cholestyramine lower the efficacy of diuretics therapy, thus amphotericin B and corticosteroids can reinforce hypokalemic effect of thiazide and thiazide-like diuretics

Carbonic anhydrase inhibitors interact with lithium preparations which cause lowering of diuretics effect.

Spironolactone can raise digoxin concentration in blood plasma and increase the risk of side effects development, including arrhythmia. Combined application of remedies with ACE inhibitors, indomethacin and other potassium preserving

diuretics can cause the development of hyperkalemia (especially on the background of renal failure). NSAIDs, lowering glomerular filtration and diuresis weaken diuretic activity of spironolactone.

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Anniversary

THE 70TH ANNIVERSARY OF EMINENT SCIENTIST, TALENTED DOCTOR-CARDIOLOGIST KRAVCHUN PAVLO GRYGOROVICH IS DEDICATED

70-РІЧЧЮ ВИДАТНОГО ВЧЕНОГО, ТАЛАНОВИТОГО ЛІКАРЯ-КАРДІОЛОГА КРАВЧУНА ПАВЛА ГРИГОРОВИЧА ПРИСВЯЧУЄТЬСЯ

70-ЛЕТИЮ ВЫДАЮЩЕГОСЯ УЧЕНОГО, ТАЛАНТЛИВОГО ВРАЧА-КАРДИОЛОГА КРАВЧУНА ПАВЛА ГРИГОРЬЕВИЧА ПОСВЯЩАЕТСЯ

Head of the Department of Internal Medicine № 2, Clinical Immunology and Allergology, a graduate of the Kharkiv National Medical University, student of academician L.T. Malaya, MD, PhD, Professor, Honorary Professor of KhNMU, Honored Worker of Science of Ukraine, academician of Higher Education of Ukraine P.G. Kravchun born in Novofedirivka Zaporozhye region on the 11Th of October, 1944. In 1960, he graduated from high school and enrolled in medical school, later as medical assistant P.G. Kravchun was drafted into the Soviet Army. Work paramedic military unit enables him to read the everyday life of medical practice, and it reinforces the belief in the correctness of the choice of life. In 1966, discharged from the army, he entered the medical faculty of the Kharkov Medical Institute. Education gives

him pleasure, especially in creative activities like science club. He impressed comrades of training with sincerity, kindness, and was elected monitor. It is more and more aware that medicine and research - this is his calling.

In 1972, P.G. Kravchun graduated with honors and was adopted in clinical studies in the Department of Hospital Therapy, which was led by an academician L.T. Malaya. Managed by Lyubov Trohymivna he conducts research microcirculatory changes in patients with myocardial infarction, the result of the work becomes a defense of the dissertation entitled «Violations micro-circulation and renin activity in myocardial infarction and its complications» (1975).

At the beginning of professional work fate brought P.G.Kravchun, while still a young man, with academician L.T. Malaya, and she became his teacher all his life, he owes her to achievements and successes.

From 1974 to 1979 P.G. Kravchun worked as an assistant of the Department of Hospital Therapy, and later associate of professor. He continues his research, expanding the scope of his research interests, along with clinical studies of the pathogenesis and treatment of coronary artery disease arises understand the need of studying the epidemiology of the disease and ways to prevent it. Careful studies in this area have been summarized in a dissertation on «Humoral mechanisms microhemo-dynamics and risk factors for coronary heart disease», which P.G. Kravchun successfully defended in 1996, the same year he was appointed dean of the 3rd Medical Faculty. During this period, P.G. Kravchun pays great attention to scientific work, expanding educational and organizational activities.

Professor P.G. Kravchun is a renowned physician, a cardiologist, a leading expert in the study of coronary heart disease. He organized in Kharkiv region large-scale epidemiological and preventive studies on active detection of risk factors for diseases of internal organs, which gave a significant economic impact. He organized studies that clarify the features of changes in hemodynamics, microcirculation, platelet-vascular hemostasis, blood lipid spectrum, clinical and anamnestic characteristics of the formation and progression of coronary artery disease. He made a significant contribution to the study of pathogenetic role of endothelin, endothelial relaxation factor and immune disorders in diseases of the cardiovascular system, which allowed the development of a reasonable therapy, primary and secondary prevention. P.G. Kravchun conducted long-term research to provide a framework thrombolytic therapy of ischemic and reperfusion injury. He researched changes in sympathetic, renin-angiotensin-aldosterone, kallikrein-kinin systems, endothelin-1, 3 - endorphin, natriuretic substances in arterial hypertension and congestive heart failure. He provided schemes of drug treatment and prevention of inhibitors of angiotensin converting enzyme and receptor angiotensin antagonists II resistance. His studies are of great scientific and practical importance, marked the depth of scientific development, widespread adoption across the Ukraine and foreign countries.

P.G. Kravchun constantly improving teaching and lecturing skills, a lot of work with young assistants, who came to the department, manages the work of masters, medical residents, graduate students: domestic and foreign. Under his leadership, the department started teaching series «Clinical Immunology». High academic scholarship, a deep knowledge of the subject and a good command are attracted to students, they are happy to listen to his lectures, attend practical classes.

From 2000 to 2007, Professor P.G. Kravchun - Vice Rector on scientific - pedagogical work in Kharkiv State Medical University.

In 2001, P.G. Kravchun was awarded the title of professor. Since 2003 he has headed the department of hospital therapy, which in 2008 renamed the Department of Internal Medicine № 2, Clinical Immunology and Allergology. Active position leads him to implement new pedagogical approaches. The department under his leadership created computer multimedia applications in cardiology, pulmonology, gastroenterology, nephrology and immunology. This positively affects the quality of teaching therapy helps conduct an objective assessment of student learning.

P.G. Kravchun's work is not only among the students, he always takes care of patients. He is kind, sincere and sensitive person,

professional - doctor of the highest category in the specialty «Therapy», «Cardiology», «Clinical Immunology». His working days - a consultation in the intensive care unit and other departments of the City Clinical Hospital № 27, is the right choice of diagnostic approaches and therapeutic approach. He participates in clinical conferences and discussion of difficult clinical cases. For doctors and students working next to him, is a real opportunity to gain significant clinical experience.

P.G. Kravchun devoted himself humane medical profession. Casual hard work gave him the opportunity to become a prolific scholar, teacher and mentor talented.

Under the direction of Professor P.G. Kravchun defended 4 doctoral and 16 candidate's dissertations. He is the author and co-author of 12 monographs and 14 textbooks, 28 patents of Ukraine, the author of over 400 scientific papers.

In 2004, Professor P.G. Kravchun received the title of Honored Scientist of Ukraine. In 2005, P.G. Kravchun was elected academician of the Academy of Higher Education of Ukraine, in the same year - Honorary Professor KhNMU. In 2006, for many years of scientific and pedagogical work, and for the achievement of the organization of the department Prof. P.G. Kravchun was awarded the highest award of Higher Education of Ukraine - Yaroslav Mudryi Award. Textbook labeled with the Ministry of Health of Ukraine «Unstable angina: clinical manifestations, diagnosis, differential treatment», edited by P.G. Kravchun in 2007, was awarded the degree of Higher Education of Ukraine. In 2008, P.G. Kravchun prizewinning of Higher Education of Ukraine for many years of hard work in high school and a significant scientific achievement. In 2003, 2004, 2005 and 2007 was awarded by the Ministry of Health of Ukraine. Repeatedly awarded diplomas of Rector of KhNMU for achievements in scientific, methodological and educational work, Diploma of Kharkov city administration and the Kharkiv Regional State Administration (2003, 2005 y.y.)

Professor P.G. Kravchun is a member of the Specialized Scientific Council of KhNMU, Academic Council of IInd Medical Faculty, chairman of the methodological commission of KhNMU in Therapy, a member of the editorial board of «Vrachebnaya practica» (Kharkiv), Deputy Chairman of the Association of Internists of Ukraine, Deputy Academician-Secretary of the Department of Medical Sciences of Higher Education of Ukraine.

Teaching staff of the Department of Internal Medicine № 2,
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