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THE STUDY OF THE INFLUENCE OF THE INFUSION FROM RUBUS CAESIUS LEAVES THE PERMEABILITY OF RATS' VASCULAR WALLS

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***Abstract**. The article describes the results, achieved from the research on the influence of the infusion from Rubus caesius leaves on the penetrability of rats' vascular walls. It was found the capillary strengthening activity of infusion due to the presence of flavonoids quercetin, kaempferolandrutin. The results obtained comply with scientific data, substantiating the statistically-valid fact that the infusion from Rubus caesius leaves can decrease vascular penetrability under the "protein", "xylol" or "formalin" inflammations.*

***Keywords:** Rubus caesius, the capillary strengthening activity, hemostatics, inflammation.*

The broadening range of hemostatics is motivated by various factors, such as: post-surgery complications, intake of different medicaments, disturbing the fusion of coagulation factors or stimulating fibrinolysis, the effect of radiotherapy and increased allergisation of population, resulted from practice of chemical therapy. One of the ways to solve this problem is to produce new hemostatics and remedies, strengthening capillaries without side effects. In this view, medicaments, based on herbal substances, are rather prospective, gaining more and more popularity in the market of drugs.

The Rubus caesius, well-known for its therapeutic qualities for a long time, was mentioned by Theophrastus, Avicenna and Dioscorides. To achieve therapeutic effect ancient healers used it as decoctions and infusions of berries, leaves and roots. The multifarious chemical composition of Rubus caesius leaves may predetermine its manifold application [1]. According to scientists, leaves of the Rubus caesius exert a hemostatic, astringent, sudorific, analgesic and anti-inflammatory effect, as well as show an antiseptic effect and accelerate digestion [2, 3].

Being substantial for hemostasis, a vascular wall is the first to react to injuries through reflex contraction, leading to deflation of blood flow to a traumatic area. Apart from that, this wall serves as a source of tissue thromboplastin and other thrombogenic factors. A vascular wall makes a biosynthesis of adrenaline, noradrenaline, lipoids, heparin and other physiologically active substances, participating in bleeding control [4].

The influence, exerted by herbal drugs on human organism through a group of biologically active substances and microelements, is manifold [5]. Consequently, it is a topical issue in modern pharmacology to seek and develop new hemostatics of a plant origin, which apart from being specifically hyperactive would be convenient and safe in application.

The purpose of our research was to investigate the influence of the infusion from the Rubus caesius on the permeability of rats' vascular walls.

Materials and Methods. The experiment was conducted on 12 WAG line rats (weight 180-200 g), kept on a standard vivarium diet. All experimental animals were raised in the vivarium in the Central research laboratory of the National Pharmaceutical University and standardized according to physiologic and biochemical criteria.

The experiment was conducted in vivo. Animals were divided into 2 groups, 6 animals in each of them: experiment and control. The experiment lasted 1 month. The infusion from Rubus caesius leaves was orally intragastrically administered to the animals from the experiment group on a daily basis (12ml/kg). Water, equivalent to the weight of the control animals, was given to the latter. As soon as the experiment came to an end, on the 30th day local inflammation was stimulated in the animals of both groups by the P.P. Golikov method with use of different phlogogenic substances, such as: egg albumin (protein), xylol, histamin and formalin [6].

The number of animals and their group distribution conformed to economical approach, bioethical rules and statistic requirements. Recalculation of human doses for the rats was conducted by Yu. R. Rybolovlev using the ratio of species sensitivity

[7]. A daily average dose for a patient makes 200 ml of the infusion, prepared in an amount of 1:10, assuming that ml/kg = 2,9.

Statistical calculations were performed by conventional methods [8].

The laboratory animals employed in the research were kept in the experimental biological clinic of the KhNMU under Storage, Care and Feeding Norms, conforming to the principles of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1986) [9] and the resolution of the First National Congress on Bioethics (Kyiv, 207) [10]. The experiments were carried out in the morning, because according to scientists this time of day shows the dependence of the main pharmacological parameters and pharmacological activity of the herbal product under study on circadian rhythms [11, 12].

Results and Discussion. The animals from the control group presented faster colouring of skin papules, produced by protein (1,8 min), slower colouring – by histamine (2,8 min) and formalin (3,4 min) and the slowest one – by xylol (4,2 min) (Table 1).

Table 1.

The capillary strengthening activity of the infusion from Rubus caesius leaves, with dose of 12 ml/kg (n = 6)

№gr.	Groups of animals	The duration of skin staining (in minutes) under the influence of phlogogenic agents			
		Egg albumin	xylol	histamin	formalin
1.	Control	1,80 ± 0,49	4,20 ± 0,73	2,80 ± 0,66	3,40 ± 0,29
2.	The infusion from Rubus caesius leaves	3,60 ± 0,68*	6,201 ± 0,58*	2,80 ± 0,37	6,80 ± 0,80*

Note: * - difference is statistically significant: versus control.

As compared to the control group, the infusion from Rubus caesius leaves with a dose of 12 ml/kg stabilized vascular walls when the level of their penetrability was raised by protein (twice), xylol (in 1,5 times) and formalin (twice). The results of the experiment show that the infusion from Rubus caesius leaves can reduce vascular penetrability under the protein, xylol and formalin inflammations (Table 1).

The obtained results attest to the fact that the infusion possesses a capillary strengthening effect and conforms to scientific data, showing the ability of such flavonoids as quercetine, kaempferol and rutin (contained in leaves of the Rubus caesius) to reduce the penetrability of walls in blood vessels (the so-called R-vitamin activity) [13].

The given method of studying the penetrability of rats' vascular walls being based on simulating local inflammation by phlogogenic substances, we can assume to a certain degree that the infusion from Rubus caesius leaves performs an anti-inflammatory activity. During inflammation, induced in rats by histamin, there was no positive effect on stabilization of the vascular wall after infiltration of the infusion from Rubus caesius leaves. This fact allows us to assume that the infusion has no anti-allergic properties.

Conclusions: 1. The infusion from leaves of the Rubus caesius produces a general strengthening effect on the permeability of blood vessel walls in rats.

2. Leaves of Rubus caesius are perspective raw materials for studying for the purpose of its application in phytotherapy.

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Резюме. Стаття представляє результати дослідження впливу настою листя ожини сизої на проникність стінок судин у щурів. Було встановлено, капілярозміцнюючу дію настою, яка обумовлена наявністю флавоноїдів кверцетин, кемпферол, рутин. Отримані результати узгоджуються з даними літератури та підтверджують здатність настою листя ожини сизої статистично вірогідно знижувати судинну проникність при «білковому», «ксилоловому», «формаліновому» запаленнях.
Ключові слова: ожина сиза, капілярозміцнююча активність, гемостатичні засоби, запалення.

Резюме. Статья представляет результаты изучения влияния настоя листьев ежевики сизой на проницаемость стенок сосудов у крыс. Было установлено капилляроукрепляющее действие настоя, обусловленное наличием флавоноидов кверцетин, кемпферол, рутин. Полученные результаты согласуются с данными литературы и подтверждают способность настоя листьев ежевики сизой статистически достоверно снижать сосудистую проницаемость при «белковом», «ксилоловом», «формалиновом» воспалениях.
Ключевые слова: ежевика сизая, капилляроукрепляющая активность, гемостатические средства, воспаление.

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THERAPY

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CHRONIC OBSTRUCTIVE PULMONARY DISEASE: ROLE OF URGENT ASPECTS OF DIAGNOSIS AND PROGNOSIS.

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Abstract. *Currently, chronic obstructive pulmonary disease (COPD) is one of the leading pathologies, leading to the quick disability of patients and a significant reduction in quality of life. Wadeley risk factors such as age, Smoking history, previously transferred diseases of the respiratory system, the harmful factors of production and living conditions. In this work the study of the relationship between factors such as Smoking history, change of body mass index, indicators of pulmonary function tests, as well as subjective evaluation tests.*
Key words: *chronic obstructive pulmonary disease, CAT scale, mMRC, 6-minute walk test, alpha 1-antitrypsin.*

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the world, after cardiovascular system disorders, infections, such as HIV-AIDS, and cancer. According to statistics, chronic obstructive pulmonary disease affects about 6% of the Ukrainian population. The development of COPD is slow, that is why this disease is often diagnosed first only in the age of 40 years and older [1, 2]. COPD is defined as an inflammation of airways characterized by persistent airflow limitations. This diagnosis now encompasses such known terms as "chronic bronchitis" and "lung emphysema". The proportion of COPD among the leading causes of death is progressively increasing. At the same time, the awareness of this problem in the society is low, and the funding allocation for COPD research studies is on the 13th place only. Only one-half of all patients with COPD have clinical diagnosis. The economic burden of this disease is enormous: according to the data available in 2011, COPD is responsible for one fifth of all cases of disability, with an

average age of retirement in the affected population reduced by 11 years [3-5]. At present, COPD is responsible for medical, social and economic losses in the entire global community, and these losses are probably even more pronounced in Ukraine.

Typical symptoms of the disease include coughing with production of mucus/sputum/phlegm and regular breathing problems (dyspnoea). The main feature of the disease is that a "simple" cough eventually progresses to acute and chronic respiratory failure, and dyspnoea starts to cause significant discomfort. As a result, one-third of patients with COPD develop apnoea, i.e. cessation of breathing during sleep [6−7].

The COPD Assessment Test was recently developed to assess health status in patients with COPD. However, little was known about its application to patients with interstitial lung disease, so we examined the relationship between the COPD Assessment Test score and respiratory impairment including the clinical picture in subjects with interstitial lung disease

It should be remembered, that genetic predisposition is also an important causative factor of COPD. This is supported by the fact that not all long-term smokers develop COPD [11-13]. However, smoking accelerates the onset of disease. Dyspnoea develops by the age of 40 in smokers and 10-15 years later in people who do not smoke [12−14].

Study object and methods. Our study group included 30 patients with COPD hospitalized in the Pulmonology unit of the Kharkiv Regional Hospital at the Department of Propedeutics of Internal Medicine No.2 and Nursing Care of the Kharkiv National Medical University. The control group consisted of 12 apparently healthy volunteers. The comparison group consisted of 10 subjects with chronic bronchitis and bronchial asthma. COPD was defined according to the order of the Ministry of Health of Ukraine No.555, corresponding to the diagnosis code J44 in ICD-10 according to statistical reports, and according to the 2011 Global Initiative for Chronic Obstructive Lung Disease (GOLD). General examination included measurements of anthropometric data such as height, weight, waist circumference, and calculated body mass index (BMI). Smoking duration was expressed in a number

of pack-years calculated by the formula (number of cigarettes × smoking duration/ 20).

A survey of patients with COPD (CAT scale, mMRC), and the 6-minute walk test (6MWT) were performed.

When studying the respiratory function, the most accessible and informative indicators to assess the severity of airway obstruction, severity and stage of progression of COPD, is forced expiratory volume during the first second (FEV1), forced vital capacity of the lungs (FVC) and the FEV_1/FVC ratio. According to the current recommendations, a diagnostic criteria for COPD is considered to be decrease of FEV_1 <80% of the norm, combined with FEV_1/FVC ratio <70%, indicating a non-fully reversible bronchial obstruction.

Thus, the main group included 19 men (72%) and 11 women (28%), with average age of 64.4 ± 4.6 years (men 65.9 ± 3.9, women 63.2 ± 3.6, respectively). The control group included 8 men (68%) and 4 women (32%) with average age of 67.2 ± 3.7 years (men 68.3 ± 3.6, women 65.1 ± 2.8, respectively). Patients in the main group had group B and D. Among them, COPD – group B was diagnosed in 15 patients and group D in 15 patients. Almost all patients complained about coughing with scarce sputum expectoration and dyspnoea of varying degrees of severity.

We analysed the data concerning smoking duration, body mass index (BMI), respiratory function, 6MWT, mMRC and CAT (Table 1). The Patients of the main group were further divided into 2 subgroups (COPD –B and COPD - D).

Analysis of the data obtained showed that compared to the respective parameters of the control group, statistically significant differences were obtained for the following parameters: smoking duration in patients with II and III Stage COPD was significantly higher than in the control group, BMI and respiratory function values in patients of the subgroup 2 were significantly lower compared with the control, while exercise tolerance in patients of the subgroups 1 and 2 were equally lower than in the control. When assessing dyspnoea according to the mMRC scale, it was observed that it was almost equally severe in both subgroups, irrespective of the disease stage and gender of patients. The CAT test results indicated significant

differences in patients with COPD - B where the average score was significantly lower than in the control group.

Table 1.

Smoking duration, BMI, respiratory function, 6MWT, mMRC, CAT

Parameters	Main group		Control group
	subgroup 1 (n=15)	subgroup 2 (n=15)	(n=12)
Smoking duration (pack-years)	25.1±2.4*	37.7±2.9*	5.9±4.7
	Men−38.4±2.9 Women−24.4±2.8		
BMI (kg⁄m^2)	25.1±1.7	20.6±3.1*	25.6±1.8
	Men−22.9±2.6 Women−27.1±1.4		
PFT (% of the norm)	FEV_1−74.6±1.5 VC−85.7±2.4	FEV_1−54.6±2.9* VC−59.6±1.8*	FEV_1−85.4±0.6 VC−93.5±2.7
6MWT	247.3±24.4* Men−252.4±22.5 Women−223.6±10.1	147.9±15.4* Men−137.2±11.6 Women−155.9±15.7	349.2±13.8 Men−374.5±20.6 Women−179.9±12.3
mMRC	Stage II −6 patients (40%) Stage III −9 patients (60%)	Stage II −4 patients (15%) Stage III −11 patients (85%)	----
CAT (score)	Men−13±3* Women−19±2*	Men−26±9 Women−28±2	Men−31±2 Women−36±2

*−$p<0.05$ *vs.* Control

Conclusions: Long-term smoking duration and the trend to decrease in IMT in the patients with COPD may be suggested as predictors of the disease progression as defined by a decline in respiratory function, exercise tolerance and progression of symptoms of pulmonary disease. The CAT scores were categorized into low, medium, high, and very high impact, and users of the CAT proposed descriptive scenarios, as the clinical picture of COPD and possible management considerations, according to the impact of COPD

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Резюме. В даний час хронічне обструктивне захворювання легень (ХОЗЛ) є однією з провідних патологій, що ведуть до швидкої інвалідизації пацієнтів і значного зниження якості життя. Виділяють такі фактори ризику, як вік, стаж тютюнопаління, перенесені захворювання дихальної системи в анамнезі, шкідливі фактори виробництва та умов проживання. В даній роботі проведено дослідження взаємозв'язку між такими факторами, як стаж тютюнопаління,

зміна індексу маси тіла, показниками функції зовнішнього дихання, а також суб'єктивними оцінними тестами.
Ключові слова: хронічна обструктивна хвороба легень, САТ масштаб, mMRC, 6-хвилинний тест ходьби, альфа-1-антитрипсину.

Резюме. В настоящее время хроническое обструктивное заболевание легких (ХОЗЛ) является одним из лидирующих патологий, ведущих к быстрой инвалидизации пациентов и значительному снижению качества жизни. Ваделяют такие факторы риска, как возраст, стаж курения, ранее перенесенные заболевания дыхательной системы, вредные факторы производства и условий проживания. В данной работе проведено исследование взаимосвязи между такими факторами, как стаж курения, изменение индекса массы тела, показателями функции внешнего дыхания, а также оценочными субъективными тестами.
Ключевые слова: хроническое обструктивное заболевание легких, mMRC, 6-минутный тест ходьбы, альфа-1-антитрипсин.

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THE INFLUENCE OF INTERLEUKIN-1β, CARBOHYDRATE AND LIPID METABOLISM ON FORMATION OF MYOCARDIAL DIASTOLIC DYSFUNCTION IN TYPE 2 DIABETES MELLITUS

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Abstract. *A total of 102 patients with type 2 diabetes and preserved left ventricular systolic function were examined in the endocrinology department of Kharkiv Regional Hospital. The following indexes were evaluated: body mass index, waist circumference, hip circumference, indexes of carbohydrate and lipid metabolism, and the concentration of IL-1β. All patients underwent echocardiography along with the determination of parameters of diastolic function. The results of statistical analysis showed that level of interleukin-1β, age, body mass index, waist to hip circumference ratio and the level of low-density lipoprotein take part in the formation of diastolic dysfunction.*

Keywords: *type 2 diabetes mellitus, body mass index, interleukin-1β, diastolic dysfunction.*

Type 2 diabetes mellitus (T2DM) is one of the major risk factors for cardiovascular disease. This effect is realized by a deterioration of the coronary arteries and myocardium as a result of the development of diabetes-specific microangiopathy, macroangiopathy, metabolic disorders and diabetic autonomic neuropathy [1, 2].

Diabetic cardiomyopathy is the specific myocardial injury, which develops in patients with T2DM independently of coronary heart disease and hypertension. The early manifestation of diabetic cardiomyopathy is left ventricular diastolic dysfunction (DD) [3, 4, 5]. The main role in the development of cardiovascular lesions in T2DM, due to the development of micro- and macroangiopathy belongs to insulin resistance, hyperinsulinemia and compensatory hyperglycemia, which launch a number of pathological mechanisms [6, 7]. As a result of these changes the basic

metabolic processes in the body are deranged, including metabolism of carbohydrates, fats and proteins. Also growth and differentiation of cells, DNA synthesis, regulation of gene transcription, etc., are broken. [8, 9]. The risk of myocardial pathology increases several times when T2DM is combined with other metabolic disorders.

A large group of cytokines, including interleukins, along with other systems provides a regulation of the basic functions in normal and pathological conditions. Interleukin-1β (IL-1β) belongs to the group of pro-inflammatory interleukins that are directly involved in the pathogenesis of cardiovascular disease because of their cytotoxic effect on the myocardium [10]. According to the experimental studies, IL-1β inhibits the contractility of myocardium in vitro models of isolated heart as well as in the culture of cardiomyocytes, promotes left ventricular remodeling, induces apoptosis of cardiomyocytes, and deranges the heart muscle function in heart failure. IL-1β is able to quickly suppress the potential-dependent calcium channels in rat ventricular cardiomyocytes and to decrease myocardial contractile function [11]. In recent years, evidence appeared that DM-2 is associated with an imbalance of certain cytokines, including the rise of IL-1β [12]. In addition, some scientists believe that activation of cytokines from the early stages of the formation of insulin resistance syndrome is the severity marker and predictor of metabolic disorders and cardiovascular disease [13]. Therefore, in recent years, considerable attention of researchers is focused on the elucidation of pathophysiological role of cytokines in the pathogenesis of cardiomyopathy in patients with T2DM [13, 14]. However, the role of IL-1β in the development and progression of diabetic cardiomyopathy in its early stages as well as in the stages of active formation of complications remains poorly understood.

Even the initial metabolic abnormalities contribute to the development and progression of diabetic cardiomyopathy in patients with T2DM who are overweight or have an abdominal obesity [7, 15]. However, the combination of various pathological factors of myocardial damage is still poorly understood in patients with T2DM and overweight.

The **purpose** of our study was to determine the correlation between the state of lipid and carbohydrate metabolism, proinflammatory IL-1β and indices of diastolic myocardial function in patients with T2DM.

Methods. A total of 102 patients at the age between 35 and 65 years with moderately severe T2DM were examined in endocrinology department of Kharkiv Regional Hospital. Duration of diabetes: 1-9 years, no severe diabetic complications were observed. The control group included 20 healthy individuals of corresponding age.

The following parameters were determined in examined patients: body weight, height, waist and hip circumference with subsequent calculation of body mass index (BMI) using the formula:

$$\text{BMI (kg/m}^2\text{)} = \text{weight (kg)} / \text{height (m}^2\text{)}$$

Type of adipose tissue distribution was defined according to the waist to hip circumference ratio (WHR).

For the purpose of our research all patients were tested for serum glucose by glucose-oxidase Somogyi-Nelson assay by the standard method; the level of glycosylated hemoglobin (HbA1c) - kinetic method using a set of reagents «DAC-Spectro Med»; total cholesterol (TC) and triglycerides (TG) - enzymatic photometric method using a set of «DAC-Spectro Med»; high density lipoprotein (HDL) - precipitation/enzymatic-photometric method using a set of «DAC-Spectro Med»; the level of low density lipoprotein (LDL) was calculated by the Friedewald's formula. The content of IL-1β was determined by immune-enzyme assay using "Vector-Best" set of reagents.

The following DD indices were determined as markers of diabetic myocardial injury by echocardiography by universally recognized method according to the recommendations of the American Cardiology Society [16]: maximum peak of diastolic filling velocity during rapid filling of the left ventricle E, the maximum peak of diastolic filling velocity of the left ventricle during systole of the left atrium A, E/A ratio, duration of isovolumetric relaxation of myocardium IVRT, deceleration time DT. The study included patients with ejection fraction above 50%.

Examined patients were divided into 2 groups that differed by the degree of left ventricular DD according to the classification by cluster analysis methods. Classification tree method has revealed that the threshold for the distribution of patients into groups was BMI 28.47 kg/m^2. In case of BMI <28.47 kg / m^2 and systolic blood pressure below 150 mm Hg patient was attributed to the group 1 (n = 38). Group 2 included patients with BMI > 28.47 kg/m^2 and average hemodynamic blood pressure above 97.38 mm Hg (n = 64 patients) [17].

Correlation analysis was performed among all studied parameters according to their distribution law using Statistica 6,0 licensed program.

During this clinical study we followed the safety precautions for the patients' health, the protection of their rights, human dignity and ethical standards in accordance with the principles of the Helsinki Declaration of Human Rights, the European Convention on Human Rights and Biomedicine, and applicable laws of Ukraine.

Results. While comparing the received data, we found significant differences in selected groups not only in comparison with the control group, but also between patients of the 1st and 2nd groups. The details are shown in the table 1.

In terms of the objectives and purpose of the study, of course, we were interested in 2nd group of patients. The determination of correlation dependencies in this group between parameters of diastolic function and BMI, WHR, serum glucose, HbA1c, TC, HDL, LDL, TG, and IL-1β showed the presence of significant negative relation between E/A and IL-1β (R = -0,27 (p <0.05)), and significant positive relation between DT and IL-1β (R = 0,274 (p <0.05)).

However, the correlation coefficients in this case were small (R <0,4), which corresponds to a weak link according to Chaddock's scale. Therefore, we used the method of multiple correlation - multiple regression in this study in order to determine the influence of IL-1β, lipid and carbohydrate metabolism, some data of objective examination on the formation of the basic indexes of diastolic function. The results of multiple regression can be represented as regression equation and the coefficient of determination R^2, which reflects the adequacy of the regression model.

Table 1.

Mean values of indices in the study groups

Investigated indices	Control group (n=20)	Group1 (n=38)	Group 2 (n=64)
Age, years	51,3±1,7	51,45±0,98	53,05±0,74
BMI, kg/m^2	23,73±0,29	25,42±0,51	33,6±0,69*/**
WHR	0,82±0,017	0,84±0,01	0,91±0,01*/**
Serum glucose, mmol/L	5,5±0,1	9,92±0,6*	9,61±0,3*
HbA1c, %	4,92±0,048	8,11±0,3*	8,45±0,23*
TC, mmol/L	4,06±0,05	4,58±0,16	5,68±0,18*/**
TG, mmol/L	1,3±0,035	1,54±0,05*	1,87±0,05*/**
HDL, mmol/L	1,39±0,02	1,2±0,02*	1,19±0,025*
LDL, mmol/L	2,01±0,045	2,65±0,16*	3,62±0,174*/**
IL-1β, pg/ml	8,12±0,24*	11,34±0,25*	14,76±0,28*/**
MV, E/A	1,4±0,075*	0,93±0,04*	0,82±0,022*/**
IVRT, ms	79,75±1,73*	102,84±1,47*	106,44±0,94*/**
DT, ms	182,2±3,68*	232,47±3,54*	239,75±2,25*

Note:
1. * significantly (p<0,05) differs from the control group
2. */** significantly (p<0,05) differs from group 1 and control group

Accordingly, the regression equations for them are as follows:

E/A = 0,75 -0,43 «Age» - 0,30 «BMI» - 0,27 «WHR» - 0,13 «IL-1β»

DT = 1,44 +0,32 «Age» +0,29 «LDL» - 0,11 «IL-1β»

The coefficient of determination R^2 in the first case was equal to 0.62, and in the second case - 0.66. This indicates a good adequacy of the regression model, i.e., 61% and 66% of changes of the dependent variables (E/A and DT) are stipulated by the influence of indices included in the equation.

Unfortunately, it didn't work to get regression equation with a high degree of adequacy for IVRT parameter. In addition, we didn't receive regression model with a reasonable degree of adequacy for the 1st group and control group.

Conclusions.

The activity of proinflammatory IL-1β increases at the beginning of T2DM and is probably one of the pathogenetic mechanisms of diabetic complications. The received data indicate that IL-1β may be considered as a mediator of myocardial damage and its progression marker in patients with T2DM and BMI above 28.47 kg/m^2, which extends the diagnostic and prognostic capabilities when examining these patients.

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Резюме: В ендокринологічному відділенні КЗОЗ «ОКЛ – ЦЕМД та МК» обстежено 102 хворих на цукровий діабет 2 типу зі збереженою систолічною функцією лівого шлуночка. Було визначено індекс маси тіла, окружність талії, окружність стегон, показники вуглеводного, ліпідного обмінів, а також концентрація інтерлейкіну-1β. Всім хворим було проведено ехокардіографічне дослідження з визначенням показників діастолічної функції. В результаті статистичного аналізу встановлено, що у формуванні діастолічної дисфункції беруть участь рівень інтерлейкіну-1β, вік, індекс маси тіла, відношення окружності талії до окружності стегон, а також рівень холестерину ліпопротеїнів низької щільності.
Ключові слова: цукровий діабет 2 тип, індекс маси тіла, інтерлейкін-1β, діастолічна дисфункція.

Резюме: В эндокринологическом отделении КУОЗ «ОКБ – ЦЭМП и МК» обследованы 102 больных сахарным диабетом 2 типа с сохраненной систолической функцией левого желудочка. Были определены индекс массы тела, окружность талии, окружность бедер, показатели углеводного, липидного обменов, а также концентрация интерлейкина-1β. Всем больным было проведено эхокардиографическое исследование с определением значений диастолической функции. В результате статистического анализа установлено, что в формировании диастолической дисфункции у больных сахарным диабетом 2 типа участвуют уровень интерлейкина-1β, возраст, индекс массы тела, отношение окружности талии к окружности бедер, а также уровень холестерина липопротеинов низкой плотности.
Ключевые слова: сахарный диабет типа 2, индекс массы тела, интерлейкин-1β, диастолическая дисфункция.

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IMMUNOPATHOLOGICAL FEATURES OF PSORIASIS

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Abstract. *Psoriasis, a common multifactor skin disease, has received attention as a target for new pathogenesis-oriented biologic therapies. Psoriasis is important to the clinician because it is common and has treatment implications beyond the care of skin lesions. It is important to the physician-scientist because it serves as a model for studies of mechanisms of chronic inflammation.*
In recent years, substantial advances have been made in elucidating the mechanisms of psoriasis. However, major issues remain unresolved, including the primary nature of the disease as an epithelial or immunologic disorder, the autoimmune cause of the inflammatory process, the relevance of cutaneous versus systemic factors, and the role of genetic versus environmental influences on disease initiation, progression
This review summarizes recent progress in understanding of the immunologic basis of psoriasis and shows how improved insight into disease mechanisms has already resulted in tangible benefits for patients, including the introduction of new targeted therapies.
Kay words*: psoriasis, cytokine, interleukin, treatments for psoriasis*

Despite the fact that psoriasis is a common multifactor skin disease, its definition by Ferdinand von Hebra as a distinct entity dates back only to the year 1841, and estimates of its prevalence – around 1-3 percent of population worldwide [1, 2]. Both Ukrainian and foreign researchers notice the following features of psoriasis: a chronic disease associated with characteristic skin rash in a form of epidermal and dermal papules considerable skin flaking. A psoriatic patch is formed on the basis of the impaired proliferation and differentiation of keratinocytes in combination with increases processes of angiogenesis and epidermal and dermal infiltration with mononuclear cells [3, 4]. Numerous family studies have provided compelling evidence of a genetic predisposition to psoriasis, although the inheritance pattern is still unclear [5]. The illness develops in as many as half of the siblings of persons with psoriasis when both parents are affected, but prevalence falls to 16

percent when only one parent has psoriasis and to 8 percent when neither parent is affected.

A key question concerns the autoimmune nature of psoriasis and the contribution of autoreactive T cells to the disease process. Currently available data do not support the notion that psoriasis is a bona fide autoimmune disease. Psoriasis is probably best placed within a spectrum of autoimmune-related diseases characterized by chronic inflammation in the absence of known infectious agents. The transport of T cells from the dermis into the epidermis is a key event in psoriasis. Psoriatic T cells predominantly secrete interferon-γ and interleukin-17 [6, 7].

The hypothesis of a cytokine network in psoriasis proposed a central role of proinflammatory cytokines, including TNF-α. In retrospect, this theory has been validated by the clinical success of anti-TNF therapy in the treatment of psoriasis. On the basis of the analysis of gene signatures in this disease, three predominant cytokines seem to be at play: type I interferon, interferon-γ, and TNF-α. Both TNF-α and interferon-γ also have anti-inflammatory properties; this might explain, in part, the counterintuitive clinical observation that anti-TNF therapy induces psoriasis in a minority of patients. In addition, dendritic cell–derived interleukin-23 and downstream products of helper T cells, including interleukin-17A and interleukin-22, are of considerable importance. Key cytokines in psoriasis act through a restricted set of signalling and transcriptional pathways [4, 8].

In spite of numerous studies performed, pathogenesis of psoriasis and mechanisms of its onset have not been clarified yet. Most accepted treatments for psoriasis have been developed empirically or were found by chance. However, recent insights into the immunopathogenesis of psoriasis have further elucidated the mode of action of some accepted compounds [9, 10] and have provided new treatment strategies [11, 12]. The severity of the disease usually determines the therapeutic approach. Approximately 70 to 80 percent of all patients with psoriasis can be treated adequately with use of topical therapy. Mainly for practical reasons, the vitamin D_3 analogues (calcipotriol and tacalcitol) and the topical retinoid tazarotene – all of which affect keratinocyte functions and the immune response – are in wider use than

is either anthralin or coal tar. Since most of the compounds that have been mentioned may irritate delicate areas of skin, topical corticosteroids are used in combination with those compounds, particularly in intertriginous areas [8, 9, 12].

In cases of moderate-to-severe psoriasis (e.g., affecting large surface areas), the use of phototherapy, systemic drugs, or both must be considered. Among the established regimens, various therapeutic methods may have distinct modes of action. For example, fumarates and cyclosporine are primarily immunosuppressive agents, whereas retinoids and methotrexate also target keratinocyte functions. Rational combination treatments target inflammation as well as epidermal alterations and may provide improved efficacy and safety. Thus, combinations of topical vitamin D_3 analogues with phototherapy or systemic retinoids plus psoralen and ultraviolet A phototherapy (RePUVA) are well-established treatment regimens for psoriasis [5, 10].

The evolution of a psoriatic lesion is based on a complex interplay between environmental and genetic factors that sets the scene for disease-initiating events. A cascade of events leads to activation of dendritic cells and, in turn, the generation of effector T cells that emigrates to and resides in skin tissue. Cross-talk between epithelial cells and immune cells shapes and maintains the inflammatory milieu. Research in the past decade has identified many of the checkpoints governing these processes and has lead to the development of new, highly effective targeted therapies. Although this progress is remarkable, there are still many unknowns, especially in the area of disease prevention and the development of drugs with appropriate long-term risk – benefit and cost profiles. Future research will need to tackle these challenges in order to establish therapeutic and preventive approaches that ultimately lead to improved outcomes for patients.

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Резюме. Псориаз распространенное заболевание кожи мультифакторной природы, находится под пристальным вниманием дерматологов и ученых исследователей всего мира в качестве мишени для изучения патогенеза и поиска новых методов лечения. Изучение псориаза очень важно как для дерматологов, так и для исследователей в качестве модели для изучения механизмов хронического воспаления.

В последние годы значительные успехи были достигнуты в выяснении механизмов псориаза. Тем не менее, основные проблемы остаются

нерешенными, в том числе этиология заболевания, патологические процессы в коже, иммунной системе, аутоиммунные причины воспалительного процесса, зависимость кожных проявлений от поражения других органов и систем, а также роль генетических факторов и воздействие окружающей среды на возникновение псориаза и его прогрессирование.

Представлены достижения в изучении иммунологического звена патогенеза псориаза и показано, как улучшение понимания механизмов болезни уже привело к повышению эффективности проводимой терапии.
Ключевые слова: псориаз, цитокины, интерлейкины, лечение псориаза.

Резюме. Псоріаз поширене захворювання шкіри мультифакторної природи, перебуває під пильною увагою дерматологів і вчених дослідників усього світу в якості мішені для вивчення патогенезу та пошуку нових методів лікування. Вивчення псоріазу дуже важливо як для дерматологів, так і для дослідників в якості моделі для вивчення механізмів хронічного запалення.

В останні роки значні успіхи були досягнуті в з'ясуванні механізмів псоріазу. Тим не менше, основні проблеми залишаються невирішеними, зокрема етіологія захворювання, патологічні процеси в шкірі, імунній системі, автоімунні причини запального процесу, залежність шкірних проявів від ураження інших органів і систем, а також роль генетичних факторів і вплив навколишнього середовища на виникнення псоріазу і його прогресування.

Представлені досягнення у вивченні імунологічного ланки патогенезу псоріазу та показано, як поліпшення розуміння механізмів хвороби вже призвело до підвищення ефективності терапії.
Ключові слова: псоріаз, цитокіни, інтерлейкіни, лікування псоріазу.

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IMMUNOHISTOCHEMICAL CHARACTERISTIC OF SKIN IN PATIENTS WITH PSORIASIS AND CORRECTION OF THE REVEALED DISORDERS

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Abstract. *The purpose of the research is determination of role of inhibitors of cellular cycle in pathogenesis of psoriasis and efficacy evaluation for pathogenetic mechanisms of therapy. For the purposes of study of cytological characteristic of hyperprolipherative processes at the inhibitors of cellular cycle level in skin of diseased patients with psoriasis at steady state and progressive state a biopsy of the plaque skin was performed. On the basis of this research evaluation of pathogenetic mechanisms during psoriasis at the inhibitors of cellular cycle level was realized, proteins (p16, p19, p21, p53) expression in psoriatic patient's skin before and after therapy was evaluated.*

Key words: *psoriasis therapy, Glutaxim*

Psoriasis is multifactorial dermatosis, whose pathogenesis is based on a lot of theories [1, 3]. Despite the recent years have witnessed a great number of publications, dealing with both the study of its pathogenesis and development of new methods of treatment, psoriasis still remains an important problem of dermatology.

At present, psoriasis is characterized as a systemic autoimmune process [11, 12] with the following changes in the immune status:

- lysozyme and phagocytic activity of neutrophilic reactions is inhibited;
- the complement and content of lactoferrin in blood are increased;
- the count of T lymphocytes decreases;
- changes take place in the titre of T lymphocytes, the ratio of T and B lymphocytes and immunoregulatory index as result of a decreased count of T helpers;
- the count of “zero” lymphocytes increases.

In this situation a lower level of IgG is observed too, the number of CIC increases. All these changes are also most manifested in complicated forms of the disease, a frequently recurrent process, particularly in patients with some concomitant pathology [10, 12].

Psoriatic plaques are known to form on the basis of disorders in epidermal differentiation. The latter is a very complex and highly regulated biochemical process, characterized by morphological changes in all structural components of epithelial cells. Generally accepted is the point of view that cell renewal processes play a leading part in the morphogenesis of psoriatic plaques, whose formation is based on epidermal hyperproliferation, caused by cell cycle disorders. Several phases are observed in the process of the preparation of a cell for its division and subsequent formation of two new cells: G1, G2, S, G0. The activation of sequences of cyclin-dependent kinases (CDK) is the "motor" of the cell cycle.

Proteins p16, p19, p21 and p53 inhibit or activate different CDK complexes, which are responsible for the normal course of all phases in the cell cycle. Psoriasis is characterized by intracellular pathological processes with resultant affection of the normal cell cycle, thereby increasing CDC complexes and expression of proteins p16, p19, p21 and p53, which activate these complexes. Gene p53 is one of the central components of the system, which ensures elimination of pathological cells from the organism; p53 is known as a tumour suppressor, an activator of apoptosis.

The activation of protein p53 is caused by damage of cells via signalling pathways, which control the state of cells. Protein p53 coordinates the process of reparation or induces autocytolysis. The loss of gene p53 causes an uncontrolled accumulation of genetic damages with a resultant loss of control from the part of the organism, a pathological growth of cells and death. Gene p53 produces the protein, which consists of 393 amino acids and has the electrophoretic mobility of 53 kD (hence the name of the gene and protein). Proteins p16, p19 and p21 are members of the CDC family, i.e. representatives of negative regulators of the cell cycle, which are responsible for the normal course of the cell cycle in phase G1, take part in the system of control over the cell cycle and stop reproduction of malignant cells. A

higher activity of proteins p16, p19 and p21 causes blockage of entering phase S by cells and their premature aging.

Few studies dealt with tumour markers in psoriasis [2, 4, 8]. Tumour markers Bcl-2, Ki-67, p21 and p53 were detected. The progressive stage of psoriasis revealed a high expression of Ki-67 and Bcl-2, as well as low levels of p21 and p53. A reliable increase of p53 expression in the epidermis at the stationary stage indirectly demonstrates an intensification of apoptosis processes in the epidermal layer [8]. The appearance of expression of p21 and p53 in the suprabasal layers of the epidermis gives evidence for an early beginning of keratinization of cell membranes, which as result are not able to form the normal horny layer and may facilitate the development of parakeratosis [8].

The purpose of the present study was to reveal the role of cell cycle inhibitors in the pathogenesis of psoriasis and assess the efficacy of pathogenetic mechanisms of therapy.

Glutoxim is one of promising medicines. It represents a new class of drug preparations, thiopoetins, and has unique biological effects. Owing to them it acts on the intracellular level of thiol metabolism and plays an important part in the regulation of metabolic processes in cells and tissues. The influence of Glutoxim stimulates proliferation and differentiation of normal cells and activates processes of genetically programmed death (apoptosis) of transformed cells. The drug action is realized through an increased half-life of protein p53 and with help of influence on the cascade of phosphoprotein kinases of the Ras signalling pathway. Thus Glutoxim normalizes cell metabolism and produces the cytoprotective effect. It is for these reasons that this medicine attracted our attention, when we studied therapy of patients with psoriasis. The positive effect consists in a higher efficacy of treatment of psoriasis cases owing to the fact that Glutoxim additionally increases reactivity of the organism.

Materials and methods. The study involved 120 patients, ill with psoriasis, who were divided into two groups.

– The main group consisted of 100 patients, including:

1) 50 cases with the stationary stage of psoriasis;

2) 50 cases with the progressive stage of the disease.

– The control group was composed of patients with the same diagnosis (20 cases).

The clinical picture of the disease severity was assessed by the psoriasis area and severity index (PASI), which averaged between 15 and 20 units.

Patients with psoriasis from the main (20 cases) and control (10 cases) groups underwent histological examinations of their skin before and after the multimodality treatment. Biopsy was carried out under local anaesthesia with 0.5 % solution of Novocain. The material was fixed in 10 % buffered aqueous solution of neutral formalin and Carnoy's fluid, and underwent celloidin-paraffin double embedding. Serial 5-6 mcm slices were prepared. Hematoxylin-eosin staining after Van Gieson was used in all cases.

During morphological examinations, we calculated the infiltrate volume density per square millimetre and assessed the degree of acanthosis on the basis of the visual analogue scale:

- 1st – the mild degree of acanthosis is regarded as an insignificant thickening of the epidermis; acantholytic bands spread deep into the derma up to 2/3 of the visual field (x 210, the total visual area is 0.4 mm^2);

- 2nd – the moderate degree of acanthosis is characterized by extension of acantholytic bands and their spreading into the derma, but already to the visual field edge with the above magnification;

- 3rd – the marked degree of acanthosis manifests itself by a larger number of acantholytic bands, their spreading outside the visual field and by extreme thinning of the suprapapillary layers of the epidermis.

In order to study the immunohistochemical characteristics of hyperproliferative processes at the level of cell cycle inhibitors in the skin of patients with the stationary and progressive stages of psoriasis before and after their treatment, biopsy of the skin of psoriatic plaques was carried on. Immunohistochemical examinations were performed on 5 mcm paraffin slices, which were deparaffinized by the standard

technique. The slices were incubated with monoclonal antibodies against p53 protein (DO-7), cyclin-dependent kinase inhibitor (p19-Ink4D), p16 protein ("Novocastra", UK), p21 clone 2G12) (BD PharMingen). Avidine-biotin-peroxidase complex method (ABC method) (Novostain Universal Quick Kit [NCL-RTU-QU], Novo-Castra, UK) was used for immune staining. In all cases, nuclei were counterstained with haematoxylin.

Before treatment, PASI in the patients averaged:

- at the stationary stage of psoriasis – 15.4;
- at the progressive stage of psoriasis – 18.6.

Immunohistochemistry before treatment revealed a high expression of proteins p16, p19, p21 and p53 in 30 patients. In the cases with psoriasis, expression of proteins at the stationary stage was slightly lower than at the progressive one. The conducted studies make it possible to state that the expression of cell cycle inhibitors in psoriasis increases, this fact being taken by us into consideration during the multimodality treatment of patients from the main group.

The control group patients (20 cases) received the standard therapy, which included:

- sedative drugs;
- antihistamine drugs;
- vitamins B6 and B12 – intramuscularly every other day, No.20;
- externally – 2 % salicylic ointment onto the skin.

The main group of patients (100 cases) received, against a background of the standard therapy, Glutoxim drug in the form of intramuscular injections of 1 % solution by 1 ml, No. 10.

Results. The rate of the reverse development of the disease was assessed by the following indices: infiltration, erythema, oedema, scaling, itching, excoriations.

Against a background of their treatment, all the patients from the main group reported a significant decrease of itching, they demonstrated decreases of erythema and skin infiltration in the foci of lesion as early as on the 5th day of therapy, the infiltration and erythema almost completely regressing on the 15th day of the

multimodality therapy. After the end of the therapy the foci had only secondary pigmentation. PASI after the treatment was:

- in patients with the stationary stage of psoriasis – 2.2;
- in patients with the progressive stage – 4.3.

The immunohistochemichal indices of patients with psoriasis after their treatment were as follows:

- at the stationary stage, the expression of proteins p16, p19, p21 and p53 slowly decreased from 27-32 % to 11 %, thereby demonstrating a change in the rate of apoptosis in the skin of cases at this stage;
- at the progressive stage, there was a weak and moderate expression of proteins p16, p19, p21 and p53 from 7 % to 25 % in cells of the basal and spinous layers.

These indices indicate acceleration in cell proliferation processes (acanthosis, parakeratosis, hyperkeratosis), while a higher content of dividing cells confirms a decrease in the rate of apoptosis.

At the regressive stage, treatment with use of Glutoxim resulted in decreases of acanthosis, hypo- and hyperkeratosis (stages 1-2). A very weak expression of proteins p16 and p21, a moderate expression of protein p19 (up to 28 %) and a decreased expression of protein p53 were observed, thereby demonstrating a higher apoptic activity of keratinocytes and a decreased proliferative activity in the epidermis.

The duration of hospitalization lasted:

- for the control group of patients – 25 ± 0.4 bed days;
- for the main group of patients, whose course of treatment included Glutoxim – 20 ± 0.4 bed days.

Conclusion. Following their multimodality treatment with Glutoxim patients with psoriasis did not reveal any expression of proteins p16 and p19 in the spinous and basal layers, while the expression of proteins p21 and p53 was weak (3-5 %), these facts demonstrating a higher apoptic activity of epidermal cells and a decrease of proliferation.

The following phenomena were observed during histological studies:

- chiefly weak expression of the horny layer, in some places it had moderate hyperkeratosis;

- positive dynamics in the state of other layers of the epidermis and dermal microvasculature;

- acceleration of regression of psoriatic eruptions;

- shortening of the patients' stay at in-patient department.

Thus, the use of Glutaxim results in positive clinical and immunohistochemical dynamics and can be recommended in both in-patient and out-patient conditions.

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Резюме: Обговорюються результати вивчення імуногістохімічних характеристик гіперпроліферативних процесів на рівні інгібіторів клітинного циклу у хворих на псоріаз та оцінки патогенетичних механізмів сучасних методів терапії. Виявлено підвищення експресії білків p16, p19, p21, p53 в шкірі хворих на псоріаз. Розроблено нові імуногістохімічні тести для вибору терапії та оцінки прогнозу перебігу псоріазу. Якщо в процесі проведеної комплексної терапії експресія білків p16, p19, p21, p53 не знижується, то це свідчить про неефективність проведеної терапії, а також говорить про несприятливий перебіг псоріатичного процесу. Якщо в міжрецидивний період до появлення нових висипів на шкірі спостерігається підвищена експресія білків p16, p19, p21, p53, це свідчить про початок рецидиву і вимагає призначення противорецидивного курсу терапії.
Ключові слова: псоріаз, терапія, Глутоксим

Резюме: Обсуждаются результаты изучения иммуногистохимических характеристик гиперпролиферативных процессов на уровне ингибиторов клеточного цикла у больных псориазом и оценки патогенетических механизмов современных методов терапии. Выявлено повышение экспрессии белков p16, p19, p21, p53 в коже больных псориазом. Разработаны новые иммуногистохимические тесты для выбора терапии и оценки прогноза течения псориаза. Если в процессе проведенной комплексной терапии экспрессия белков p16, p19, p21, p53 не снижается, то это свидетельствует о неэффективности проведенной терапии, а также говорит о неблагоприятном течении псориатического процесса. Если в межрецидивный период до появления новых высыпаний на коже наблюдается повышенная экспрессия белков p16, p19, p21, p53, это свидетельствует о начале рецидива и требует назначения противорецидивного курса терапии.
Ключевые слова: псориаз, терапия, Глутаксим

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THE EFFECT OF TREATMENT WITH TRIMETAZIDINE ON THE COURSE OF ARRHYTHMIA IN PATIENTS WITH ISCHEMIC HEART DESEASE AND DIABETES MELLITUS

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Abstract. *It was studied the effect of trimetazidine in patients with ischemic heart disease and diabetes mellitus with concomitant cardiac arrhythmias: ventricular and supraventricular extrasystoles and cardiac fibrillation. It was investigated 35 patients, among them 12 with registered supraventricular extrasystoles, 12 with ventricular extrasystoles, 11 patients with paroxysmal form of cardiac fibrillation. It has been shown that the treatment with trimetazidine is accompanied by decreasing of the number of supraventricular and ventricular extrasystoles in patients with ischemic heart disease and diabetes mellitus 2 type. The treatment with trimetazidine is accompanied by the reduction of severity of myocardial ischemia.*
Key words: *arrhythmia, trimetazidine, chronic ischemic heart disease, diabetes, lipid, carbohydrate metabolism.*

At last time, much attention is given to drugs that have a positive effect on the metabolism of ischemic myocardium [1, 10]. Some drugs in this group, not having electrophysiological properties have antiarrhythmic effect by influencing on the different mechanisms of arrhythmogenesis [3, 5], including myocardial fibrosis, left ventricular remodeling. Indirect antiarrhythmic properties of drugs of metabolic actions serve as an additional argument in favor of their appointment in patients with ischemic heart disease, including patients with concomitant diabetes mellitus.

Among the drugs of metabolic action the special interest is induced by trimetazidine [7]. Recently, the drug entered in the arsenal of preparations that are used to treat patients with ischemic heart disease and concomitant diabetes mellitus. Trimetazidine selectively inhibits the enzyme 3-ketoacyl-KoAtiolazu and causes a partial decrease of β-oxidation of free fatty acids [7, 8]. It is noted the increasing of

glucose metabolism, increasing of formation of adenosinediphosphate, the improving of myocardial contractility [4, 11]. In patients with diabetes mellitus trimetazidine optimizes the myocardial metabolism by restoring the balance between glycolysis and glucose oxidation [4, 11]. This results in a more economical way of the oxidation of carbohydrates and reduce the manifestations of ischemia. It is important to emphasize that the drug exerts the antihypoxiaand cytoprotective effect onmyocardium, reduces the negative effect on its free-radical oxidation [9]. It is now established that free radicals contribute to the appearance of cardiac arrhythmias and cause electrical instability of the myocardium [6]. Arrhythmias are often observed in patients with coronary artery disease with concomitant diabetes, especially in the presence of myocardial dysfunction [6, 10]. With the development of clinically significant chronic heart failure, the ventricular arrhythmias are regarded as predictor of sudden death [12].

The purpose of the study. The studying of the effects of trimetazidine in patients with coronary artery disease and diabetes mellitus II types with concomitant cardiac arrhythmias: ventricular extrasystoles, supraventricular extrasystoles and cardiac fibrillation.

Materials and methods. It was examined 35 patients, among them 12 with registered supraventricular extrasystoles, 12 with ventricular extrasystoles, 11 with paroxysmal cardiac fibrillation. The age of the patients was from 48 to 63 years. The study was conducted by open way without prescribing a placebo. Trimetazidine was administered at a dose of 30 mg 3 times a day on a background of standard therapy, which included nitrates, angiotensin-converting enzyme inhibitors, disaggregants. Initially and after 3 months of treatment the electrocardiogrammonitoring was performed. Together with arrhythmias it was evaluated the number and duration of ischemic episodes with reduction of S-T segment below the isoelectric line by 1 mm or more.

Results and discussion. The results of investigation of patients are shown in table 1. After treatment with trimetazidine heart beat rate, systolic blood pressure, diastolic blood pressure did not change from baseline values. Number supraventricular

extrasystoles significantly decreased from 314,7 ± 9,4 to 168,8 ± 7,6 per day (p <0,05).

Table 1.

The results of daily electrocardiogram monitoring during the treatment with trimetazidine

Indicators	The period of observation	Group of patients		
		Supraventricular extrasystoles (n = 10)	Ventricular extrasystoles (n = 11)	Cardiac fibrillation (n = 10)
Heart beats rate / min.	Beforetreatment	76,0 ± 3,8	73,2 ± 1,2	74,1 ± 2,2
	After treatment	75,0 ± 2,3 p>0,05	74,4 ± 2,4 p>0,05	72,3 ± 3,3 p>0,05
Systolic blood pressure	Before treatment	138,4 ± 6,4	139,6 ± 5,8	130,7 ± 2,9
	After treatment	137,7 ± 7,2 p>0,05	135,7 ± 6,3 p>0,05	131,8 ± 3,8 p>0,05
Diastolic blood pressure	Before treatment	76,5 ± 2,9	72,4 ± 3,3	71,7 ± 1,9
	After treatment	74,3 ± 2,3 p>0,05	71,5 ± 2,1 p>0,05	72,8 ± 2,2 p>0,05
Number of supraventricular extrasystoles per day	Before treatment	314,7 ± 9,4	-	-
	After treatment	168,8 ± 7,6 p <0.05	-	-
The number of ventricular extrasystoles per day	Before treatment	-	892,7 ± 11,7	-
	After treatment	-	474,8 ± 12,4 p<0,05	-
The number of paroxysmal cardiac fibrillation per day	Before treatment	-	-	1,2 ± 0,4
	After treatment	-	-	1,1 ± 0,5 p>0,05
The number of episodes of S-T per day	Before treatment	4,3 ± 0,7	4,6 ± 0,8	3,1 ± 0,2
	After treatment	2,1 ± 0,6 p<0,05	2,0 ± 0,3 p<0,05	1,6 ± 0,4 p<0,05
The duration of episodes of reducing S-T, min.	Before treatment	3,3 ± 0,2	3,8 ± 0,4	3,0 ± 1,8
	After treatment	2,9 ± 0,3 p>0,05	3,0 ± 0,2 p>0,05	2,8 ± 2,2 p>0,05

A significant change in the frequency of paroxysmal cardiac fibrillation in patients was not detected (p> 0,05). The number of ventricular extrasystoles per day after treatment with trimetazidine decreased from 892,7 ± 11,7 to 474,8 ± 12,4 (p <0,05). Attention is drawn to the fact that the drug therapy was accompanied by statistically reliable significant reduction in the number of episodes of myocardial ischemia in all groups of patients regardless of the type of disturbances of heart rhythm (table. 1).

It is important to determined thecharacter of the influence of trimetazidine on the performance of renin-angiotensin-aldosterone system, lipid metabolism, the level of endotelin-1, catecholamines and cyclic guanosine monophosphate in patients with coronary artery disease and diabetes II with concomitant cardiac arrhythmias.

As it is seen from the table 2 the data of treatmentwith trimetazidine was not associated with significant changes in indicators of renin-angiotensin-aldosterone system. There were no significant changes in plasma renin activity, aldosterone, angiotensin II, electrolytes (p> 0,05) (table 2).

Table 2.

System status of renin-angiotensin-aldosterone system in patients with ischemic heart disease and diabetes mellitus II types with concomitant cardiac arrhythmias

Indicators	The period of observation	Group of patients		
		1st	2nd	3rd
		Supraventricular extrasystoles (n = 10)	Ventricular extrasystoles (n = 11)	Cardiac fibrillation (n = 10)
Activityof plasma renin ng/ml/g^{-1}	Before treatment	4,29 ± 0,42	6,32 ± 0,86	6,12 ± 0,98
	After treatment	4,31 ± 0,31 p<0,05	6,43 ± 0,9 p>0,05	6,21 ± 0,76 p>0,05
Aldosterone pg /ml	Before treatment	326,3 ± 41,2	331,8 ± 38,7	392,7 ± 29,4
	After treatment	327,9 ± 56,3 p>0,05	330,8 ± 42,9 p>0,05	397,4 ± 31,5 p>0,05
Angiotensin II pg/ml	Before treatment	17,3 ± 2,41	24,7 ± 3,2	22,4 ± 2,7
	After treatment	17,4 ± 2,52 p>0,05	23,9 ± 4,1 p>0,05	22,01 ± 2,9 p>0,05
Na^+mmol/l	Before treatment	142,7 ± 3,51	134,3 ± 2,08	137,6 ± 4,1
	After treatment	141,7 ± 4,32 p>0,05	135,6 ± 1,92 p>0,05	136,8 ± 3,9 p>0,05
K^+mmol/l	Before treatment	4,18 ± 0,15	3,76 ± 0,19	3,89 ± 0,11
	After treatment	4,19 ± 0,18 p>0,05	3,74 ± 0,18 p>0,05	3,85 ± 0,14 p>0,05

During evaluation of the influence of trimetazidine on lipid metabolism it was unable to identify any changes in the dynamics of therapy (tab. 3).

During the treatment with trimetazidine it was unable to identify its influence on the level of plasma catecholamines (tab. 4).

Table 3.

Lipid metabolism during the treatment with trimetazidine

Indicators	The period of observation	Group of patients		
		1st	2nd	3rd
		Supraventricular extrasystoles (n = 10)	Ventricular extrasystoles (n = 11)	Cardiac fibrillation (n = 10)
Total cholesterol, mmol/l	Before treatment	7, 14 ± 0,19	7, 21 ± 0,26	7,08 ± 0,17
	After treatment	7, 12 ± 0,18 p>0,05	7,18 ± 0,32 p>0,05	7, 12 ± 0,26 p>0,05
Triglycerides,mmol/l	Before treatment	2, 96 ± 0,15	3, 12 ± 0,20	2,94 ± 0, 17
	After treatment	2.9 8 ± 0,18 p>0,05	3, 16 ± 0,19 p>0,05	2,98 ± 0,21 p>0,05
Low density of lipoproteins, mmol/l	Before treatment	4,61 ± 0,16	4,94 ± 0,19	4,79 ± 0,14
	After treatment	4,62 ± 0,18 p>0,05	4,92 ± 0,18 p>0,05	4,83 ± 0,20 p>0,05
High density of lipoproteins, mmol/l	Before treatment	1,02 ± 0,05	0,70 ± 0,01	0,72 ± 0,03
	After treatment	1,03 ± 0,04 p>0,05	0,76 ± 0,02 p>0,05	0,73 ± 0,05 p>0,05

Table 4.

Catecholamine levels during the treatment with trimetazidine

Indicators	The period of observation	Group of patients		
		1st	2nd	3rd
		Supraventricular extrasystoles (n = 10)	Ventricular extrasystoles (n = 11)	Cardiac fibrillation (n = 10)
Adrenaline, mmol/l	Before treatment	5,26 ± 0,31	5,41 ± 0,25	5,32 ± 0,28
	After treatment	5,24 ± 0,32 p>0,05	5,37 ± 0,29 p>0,05	5,33 ± 0,29 p>0,05
Noradrenaline, mmol/l	Before treatment	39,41 ± 2,02	40,01 ± 1,12	39,82 ± 2,01
	After treatment	38,59 ± 3,01 p>0,05	41,02 ± 1,11 p>0,05	37,86 ± 1,92 p>0,05

The therapy with trimetazidine did not cause the significant changes in the level of plasma endotelin-1 (tab. 5), although the tendency to its decreasing was observed in all groups of patients, but it did not reach the statistically significant importance.

During evaluationof the influence of trimetazidine on cyclic guanosine monophosphateit was determined that the drug does not effect on its level in patients with supraventricular extrasystoles and cardiac fibrillation, but it is observed the

tendency to its increasing in patients with ventricular extrasystoles, although it did not reach the statistical significance (tab. 5).

Table 5.

The changes in the level of endotelin-1 and cyclic guanosine monophosphatein the course of treatment with trimetazidine

Indicators	The period of observation	Group of patients		
		Supraventricular extrasystoles (n = 10)	Ventricular extrasystoles (n = 11)	Cardiac fibrillation (n = 10)
Endotelin-1, ng/ml	Before treatment	14,12 ± 1,07	16,52 ± 0,64	15,12 ± 0,81
	After treatment	14,13 ± 0,84 p>0,05	15,84 ± 1,2 p>0,05	15,10 ± 0,94 p> 0,05
Cyclic guanosine monophosphate,nmol/l	Before treatment	6,97 ± 0,83	6,54 ± 0,67	7,01 ± 0,94
	After treatment	6,99 ± 0,91 p>0,05	7,21 ± 0,56 p>0,05	7,02 ± 0,88 p>0,05

In studying the effects of the drug on carbohydrate metabolism it was not noted its significant effect on the level of immunoreactive insulin and plasma glucose (tab. 6).

Table 6.

The indexes of carbohydrate metabolism

Indicators	The period of observation	Group of patients		
		1st	2nd	3rd
		Supraventricular extrasystoles (n = 10)	Ventricular extrasystoles (n = 11)	Cardiac fibrillation (n = 10)
Immunoreactive insulin,kED/m	Before treatment	13,4 ± 0,38	15,3 ± 0,96	14,9 ± 0,74
	After treatment	12,9 ± 0,78 p>0,05	15,2 ± 0,84 p>0,05	14,0 ± 0,76 p>0,05
Blood glucose, mmol/l	Before treatment	6, 63 ± 0,32	7, 42 ± 0,41	6,96 ± 0,51
	After treatment	6, 61 ± 0,28 p>0,05	7,39 ± 0,52 p>0,05	6,97 ± 0,29 p>0,05

Conclusions:

1. The therapy with trimetazidine is accompanied by decreasing of the number of supraventricular and ventricular extrasystoles in patients with ischemic heart disease and diabetes mellitus.

2. The drug has no effects on the incidence of paroxysmal cardias fibrillation. The treatment with trimetazidine is accompanied by a reduction of severity of myocardial ischemia.

3. The drug has no effects on the indexes of carbohydrate and lipid metabolism, the state of renin-angiotensin-aldosterone system, cyclic guanosine monophosphate, endotelin-1, immunoreactive insulin.

4. The antiarrhythmic and anti-ischemic effects of the drug are due to primarily to its effects on the intracellular metabolism in cardiomyocytes.

5. Trimetazidine inhibits □oxidation by inhibiting the metabolism of fatty acids, and this contributes to a more economical use of oxygen in the oxidation of carbohydrates and thus results in reducing the occurrence of myocardial ischemia and anti-arrhythmic action.

The study of the effect of treatment with trimetazidine on the course of arrhythmias in patients with ischemic heart disease and diabetes mellitus 2 type will be continued and studied in subsequent scientific investigations.

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Резюме. Був вивчений ефект тріметазідіну у хворих на ІХС і СДІІ з супутніми порушеннями серцевого ритму: шлуночкова, суправентрикулярна ектрасистолія і миготлива аритмія. Обстежено 35 хворих, серед яких у 12 реєструвалася суправентрикулярна екстрасистолія, у 12 шлуночкова екстрасистолія, у 11 - пароксизмальна форма миготливої аритмії. Показано, що терапія тріметазідіном супроводжується зменьшенням кількості суправентрикулярних і шлуночкових екстрасистол у хворих на ІХС і СДІІ. Лікування тріметазідіном супроводжувалося зменшенням вираженості ішемії міокарда.
Ключові слова: аритмії, тріметазідін, хронічна ішемічна хвороба серця, цукровий діабет, ліпідний обмін, вуглеводний обмін.

Резюме. Был изучен эффект триметазидина у больных ИБС и СДІІ с сопутсвующими нарушениями сердечного ритма: желудочковая, суправентрикулярная эктрасистолия и мерцательная аритмия. Обследовано 35 больных, среди которых у 12 регистрировалась суправентрикулярная экстрасистолия, у 12 желудочковая экстрасистолия, у 11 – пароксизмальная форма мерцательной аритмии. Показано, что терапия триметазидином

сопровождается урежением числа суправентрикулярных и желудочковых экстрасистол у больных ИБС и СДII. Лечение триметазидином сопровождалось уменьшением выраженности ишемии миокарда.

Ключевые слова: аритмии, триметазидин, хроническая ишемическая болезнь сердца, сахарный диабет, липидный обмен, углеводный обмен.

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INDUCED SPUTUM ANALYSIS OF INTERLEUKINS SPECTRUM IN CHILDREN WITH PULMONARY DISEASES

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***Abstract**. This article has been performed the investigation of immunity system characteristics in children with bronchitis. There has been identified factors of unfavourable prognosis of bronchitis transformation in other chronic lung diseases, which include disorder of cytokines-synthesis. A study was undertaken to determine the airway and lung inflammation, by analysing cytokines in the induced sputum from 38 children with the acute bronchitis, 35 patients with the acute pneumonia, 15 children with the chronic lung disease, which had lung fibrosis, and 18 healthy children. Sputum levels of interleukin-4 (IL-4), interleukin-6 (IL-6), interleukin-8 (IL-8) and interleukin-10 (IL-10) in all groups were statistically significantly increased compared with normal controls. The increase in the interleukins concentration in induced sputum of patient with bronchitis and pneumonia we can use in clinical as the risk subgroup of patients with chronic lung diseases.*

***Key words:** bronchitis, pneumonia, interleukin*

The underlying mechanisms of lung inflammatory response in children with the chronic lung disease has not yet been completely elucidated [1-3]. We therefore used this technique to evaluate the presence of airway and lung inflammation in children with the acute bronchitis, pneumonia, chronic lung disease. Analysis of sputum induced by inhalation of hypertonic saline has recently been established as a useful non-invasive technique for measuring airway inflammation in patients [4-5].

Aim and objectives

Aim is to improve diagnosis of immunological disorders in children with respiratory diseases, which include the study of cellular, humoral immunity and levels of cytokine (IL-4, IL-6, IL-8, IL-10) in induced sputum.

Material and methods.

The 106 patients were recruited from Regional Children Clinical Hospital (RCCH), Kharkiv, Ukrainian. The Head of RCCH is Muratov G.R., the head of pediatric department of KNMU is DMedSci, Prof. Senatorova G.S. Children with the acute bronchitis (n=38) aged on average (6,9±2,4) years who had been admitted to the pulmonology department served as group 1. The distribution in the 1 group was as follows: 21(55,0±8,0%) boys and 17(44,7±8,1%) girls. The patient with the acute pneumonia (n=35) aged on average (8,0±2,3) years served as group The constituents average are 19 (54,3±8,4%) boys and 16 (45,7±8,4%) girls. Fifteen children with the chronic lung disease (n=15), aged on average (8,0±2,3) years, which had lung fibrosis, served as group 3. The distribution in the 3 group was as follows: 6 (40±13,1%) boys and 9 (60±13,1%) girls. Healthy controls (n =18) were negative for allergies and respiratory diseases. Respiratory diseases was defined according to the Ukrainian protocol of diagnosis and treatment lung diseases in children. After clinical evaluation and immunology blood testing, induced sputum was collected. To determine the biochemical analysis of sputum induced after inhalation of hypertonic saline, we analyzed sputum induced in children subjects. The sputum was induced with inhalation of ultrasonically nebulized hypertonic (2,7-5%) saline solution. The study was approved by the ethics committee of the Kharkiv national medical university and all parents of children gave informed consent to participate in the study. We performed IL-4, IL-6, IL-8, IL-10 "IFA-Best" as previously described using a monoclonal anti-human interleukins anti-body obtained by ("IL-4-IFA-Best", "IL-6-IFA-Best", "IL-8-IFA-Best", "IL-10-IFA-Best", Russia) Statistical analysis was performed using „Stadia-6",version „Prof", „Statistica-6".

Results and discussion

We first compared IL-4 production of all groups from control subjects. Local IL-4 levels in sputum were higher in the samples of the all cases than in their controls. When compared with sputum from normal subjects sputum of patients with bronchitis (53,8 (32,3; 63,6) pg/ml, $p<0,0001$), with pneumonia (40,9 (20,4; 62,6)

pg/ml, p=0,0041), with chronic lung diseases (55,9 (53,3; 62,6) pg/ml, p<0,0001) contained a significantly higher levels of IL-4. There was statistically significant difference between sputum IL-4 levels of patients with pneumonia and with chronic lung disease (p=0,0431). This observation is inline with reports indicating a significant role of IL-4 in promoting inflammation in the lung. IL-4 increases the expression of other inflammatory cytokines from fibroblasts that might contribute to inflammation and lung remodelling in chronic respiratory diseases.

In patients the median level of IL-6 in sputum of children with bronchitis, with pneumonia and with chronic lung disease and control group were (69,1 (51,6; 85,9) pg/ml, p<0,0001), (49,4 (24,8; 79) pg/ml, p=0,0002), (55,1 (51,4; 60,7) pg/ml, p<0,0001) and 19,9(13,1; 26,3) pg/ml. There were significant differences in the sputum cytokine levels between the subjects of children with bronchitis and pneumonia (p=0,0040) and between the subjects of children with bronchitis and lung fibrosis (p=0,0415). The present data show that production of IL-6 indicating a significant role in the pathogenesis of acute inflammation.

In our study we compared IL-8 production in the sputum from control subjects and from all patients. The median and the interquartile range level of IL-8 in sputum are summarised for each age group: in the group 1 (78,1(60,5;86,5) pg/ml, p<0,0001), in the group 2 (79,4 (53,3; 88,3)pg/ml, p<0,0001), in the group 3 (90,1 (88,3; 93,8) pg/ml, p<0,0001) and in the control group (31,5(19,9; 43,3) pg/ml). Subjects of children with lung fibrosis had a significantly higher concentration of IL-8 in induced sputum than subjects of children bronchitis (p<0,0001) and subjects of children pneumonia (p<0,0001). The concentration of IL-8 in the induced sputum samples differentiated patients with bronchitis and pneumonia from patient with lung fibrosis, and indicated at risk for transformation acute diseases to chronic lung diseases.

IL-10 were significantly increased in induced sputum sample from patients of all groups compared with normal subjects. We found that induced sputum from subjects of patients with bronchitis (49,6 (38,9; 57,3) pg/ml, p<0,0001), with pneumonia (72,6 (59,4; 77,9) pg/ml, p<0,0001), with chronic lung diseases (81,5 (77,6; 85,4) pg/ml, p<0,0001) had a higher concentration of IL-10, compared to control (25,9(16,9; 30,2)

pg/ml). We found that induced sputum from subjects of patients with chronic lung diseases had a higher concentration of IL-10 compared to children with bronchitis ($p<0,0001$) and with pneumonia ($p<0,0001$), respectively. Increasing sputum levels of IL-4, IL-6, IL-8, IL-10 of all groups are indicating a role of cytokines in the remodeling process of the airways and lung.

Conclusions

Our results indicate that there is a predominant inflammation in the airways of patients with chronic lung diseases associated cytokines. The present data show that production of IL-4, IL-6, IL-8 and IL-10 in sputum, reflecting upper airway and lung inflammatory responses, was statistically significantly elevated in children with lung fibrosis, as compared to children with bronchitis and pneumonia.

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Резюме. У статті наведені результати дослідження показників імунної системи у дітей з бронхітами. Були відображені фактори трансформації бронхітів в хронічну бронхолегеневу патологію, включаючи порушення продукції

цитокінів. Дослідження визначило умови персистенціїї бронхолегеневого запалення, за допомогою вивчення концентрації цитокінів в індукованому мокротинні у 38 дітей з гострими бронхітами, у 35 дітей з пневмоніями, у 15 дітей з хронічною бронхолегеневою патологією та пневмофіброзом, та у 18 здорових дітей. При порівнянні з показниками групи контролю у пацієнтів всіх досліджуваних груп відзначалися статистично достовірно підвищені рівні інтерлейкінів (ІЛ-4, ІЛ-6, ІЛ-8, ІЛ-10) в індукованому мокротинні. Підвищення концентрації інтерлейкінов у індукованому мокротинні у дітей з бронхітами та пневмоніями, можливо використовувати в якості виявлення групи ризику у формуванні хронічної бронхолегеневої патології.
Ключові слова: бронхіт, пневмонія, інтерлейкін

Резюме. В статье представлены результаты исследования показателей иммунной системы у детей с бронхитами. Были выявлены факторы неблагоприятного прогноза и трансформации бронхитов в хроническую бронхолегочную патологию, включающие нарушение продукции цитокинов. Исследование определило факторы, способствующие персистенции бронхолегочного воспалительного процесса, с помощью изучения концентрации цитокинов в индуцированной мокроте у 38 детей с острыми бронхитами, у 35 детей с пневмониями, у 15 детей с хронической бронхолегочной патологией, имеющих пневмофиброз и у 18 здоровых детей. При сравнении с показателями группы контроля отмечалось достоверное повышение уровней интерлейкинов (ИЛ-4, ИЛ-6, ИЛ-8, ИЛ-10) в индуцированной мокроте во всех исследуемых группах. Повышение концентрации интерлейкинов в индуцированной мокроте у пациентов с бронхитами и пневмониями, можно использовать в качестве выявления группы риска формирования хронической бронхолегочной патологии.
Ключевые слова: бронхит, пневмония, интерлейкин.

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QUALITY OF LIFE AND HEALTH FACTORS AMONG WOMEN OF REPRODUCTIVE AGE IN UKRAINE

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Resume: *At the article there are aspects of medical and Gallup poll of childbearing age women of the biggest region of Eastern Ukraine. Authors elucidated a risk factors have influenced on 379 women reproductive health due to the questioning. The evaluation of medical care quality to pregnancy women was performed in Kharkiv region. The health activities of medical staff and increasing of motivation to improving proper health of women are considering it necessary for prophylactics of pregnancy losing and neonatal diseases.*
Key words: *childbearing age women, Gallup poll, adverse factors for fetus and newborn*

Quality of life (QoL) relates to an individual's perceived understanding of his or her place in life in the context of culture and environmental systems. It is a complex, multidimensional construct affected by physical, mental, social, emotional, sexual, and spiritual parameters (BJOG, HCWI). Given the range and depth of its measures quality of life can be a powerful health indicator, and quality of life assessments are increasingly being utilized to inform descriptions of population health.

Numerous reports from eastern Europe suggest that preventable health problems of women in this region may be endemic. Few data exist, however, that describe women's health in Ukraine, particularly those of reproductive age. Information gaps in Ukraine may be a consequence, at least in part, of poor routine antenatal care for pregnant women; the national Order of the Ministry of Medicine currently makes no provision for this service.

Improved understanding of the current state of women of reproductive age in Ukraine in crucial to maximizing their health antepartum, at the time of childbirth, and postpartum. In addition, there is strong evidence that maternal health has vital implications for the health of unborn fetuses and newborns, and, through developmental 'programming' even plays a potential contributing role to risk of adult-onset chronic disease.

The aim of this survey study was to (a) comprehensively describe, for the first time, the QoL and principal health factors of women of reproductive age in Ukraine; (b) analyze the results in the context of currently available health services, and (c) if necessary, develop recommendations for health system enhancements that could contribute to optimization of women's health care and improved maternal outcomes.

Methods. The investigation took place in Kharkiv, the largest administrative region of Ukraine with a general population of nearly 1.5 million. All women aged 15-41 from Kharkiv who presented to the maternity clinic at Kharkiv National Medical Hospital during 2009 were eligible for the study. The size of the sampling of population was calculated based on prior childbirth rates in Kharkiv region; in 2008, there were 24,001 live births.

A total of 379 women were randomly selected to participate. All women that were approached to participate in the survey agreed to do so and were consented. The questionnaire form used in the study was modified from validated tools used by AIHA and USAID. [4] Statistical analyses were performed with a commercial statistics package (STATISTICA 7). The study design was approved by the Kharkiv National Medical University.

Results. Respondents were mostly Ukrainians (85%). Seventy-percent of women were married, 29% were divorced, and 1% were single. The majority of women were between 21 and 30 years of age (59%).

The 67% of respondents were satisfied with their health, 18% - were not satisfied, at that 11 % have difficulties in fulfilling different kinds of activities, 12% - were not satisfied their income. Only 19% of women who are satisfied with the level of health think that their physical condition corresponds to their age or even better

than other women's condition of their age. The last three month before the women were questioned, 45% of them had had moderate pains caused by different reasons. When comparing their physical condition with the physical condition of other women of their age 74% respondents consider, that it is does not differ from the latest. 5% of women consider it to be worse comparing with other women of their age.

The breach of work conditions of women and especially of pregnant women is often underestimated as a factor for their and future babies' health. Most of questioned women in Kharkiv region are employed. Moreover 63% of them like their work. But still 28% women considered stress at work the main reason of their bad mood, 33% of women were not afraid to lose their job, 33% of respondents had fears to lose their jobs.

55 respondents out of 333 have chronic diseases. It is interesting to notice that the most of these diseases are chronic urinosexual system diseases. 27% of the women had chronic otorhynolaryngologic diseases, 16% - pathology of gastro-intestinal tract, 15% - respiratory system diseases and allergy, 6% of women had diseases of cardio-vascular system.

We received quite different results when we characterized the diseases during the pregnancy. No doubt, that the information can't be considered full, but we keep to the point that the women are more careful about their health during pregnancy. 84% of them had acute respiratory infections, and 15% of them specific pregnancy disease.

It is extremely dangerous for a pregnant to smoke or drink alcohol; it leads to a complex of syndromes of neonates, i.e. prematurely, congenital abnormalities, intrauterine growth retardation and psychic development. Unfortunately it is common for the Ukrainian society to smoke tobacco and drink alcohol. 10% of women said that they were smoking and 25% of them were drinking alcohol being pregnant. If to extrapolate this data into general sampling we get impressive figures – 2400 women who are in pregnancy smoke and 6000 women drink. Despite this fact, the physicians in their practice underestimate it, because they are not reflected properly in medical documents. The mentioned above facts are important because they are violent from

the maternal side to her fetus [6]. The questioning showed, that the half of the women who had not been smoking or drinking alcohol, had husband these bad habits.

Further we studied the conditions of women's medical care and their quality judged by the respondents. 353 women answered the question about received health care during their pregnancy. So out of all asked women 75% were examined by an obstetrician and gynecologist, 11% - by a midwife, 3% - by a family doctor, but 11% were not examined at all. The average distance to a hospital where the women were examined was 5 km (min - 0.2 km; max - 100 km). We did not receive any difference when we compared the distance from the medical office and the medical staff qualification. Every third woman in Kharkiv region uses public transport or taxi to get to the medical office, every forth woman used her own car. When learning the conditions of received medical care we knew that every third woman had to queue for a long time to be examined at the medical office. As a rule, the medical staff respectful to the women (it was marked by 62% of women) but 32% of women said that the proper norms of ethics and deontology had not been used.

We should mention that in the time of computer technologies 14% of women did not know about the places where they could receive medical care. The authors of this article pay mark that there is an operating institute of Family Planning in Kharkiv region: 63% of women are not acquainted with the methods of family planning. No doubt that just this institution lets force and prevent giving birth to children with congenital malformations and inherited pathology and then influence the infant's death and increasing of children's disability.

Discussion

Besides nowadays the main approaches in the investigation of the QoL in medicine are the following: studying the influence of diseases on physical, psychological and social functioning of a person, studying the influence functioning of treatment on the parameters of quality of a patient's life; the estimation of effectiveness of medical supplies; prognostic determination of the parameters of quality of life; QoL as a criteria of a patient's remission or recovering; individual monitoring of QoL and carrying out population social-medical investigations.

Conclusions:

1. The carried out social-medical research of the population let find out "hidden" factors which influence not only reproductive health of a woman, but also her offspring.
2. In modern society more attention should be paid to labor hygiene of a working woman, because there is close connection between woman's health condition and her labor conditions and atmosphere at work.
3. The factors analysis the revels the necessity of active actions of medical staff to prevent these factors.
4. It is necessary to active the word of the Family planning institute in the region.
5. It is evident that to prevent pregnancy loss it is necessary to raise the motivation of women to take better care of their health.

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Резюме. В статті відображені аспекти медико-соціологічного опитування жінок одного з крупніших регіонів Східної України. Опитування 379 жінок репродуктивного віку дозволило авторам виділити фактори, які впливають на репродуктивне здоров'я жінок. Виявлена питома вага шкідливих звичок, випадків загроз та насилля в сім'ї, соціологічний портрет сучасної жінки. Проведена оцінка якості надання медичної допомоги вагітним жінкам в

Харківський області. Для профілактики втрат вагітності, захворювань у немовлят необхідні заходи щодо підвищення мотивації жінки більш відповідально ставитися до власного здоров'я; існує необхідність активного втручання щодо їх попередження з боку медичних працівників.
Ключові слова: жінка репродуктивного віку, медико-соціологічне дослідження, несприятливі фактори для плоду та новонародженого.

Резюме. В статье отражены аспекты медико-социологического опроса женщин одного из крупнейших регионов Восточной Украины. Опрос 379 женщин репродуктивного возраста позволил авторам выделить факторы, которые влияют на репродуктивное здоровье. Установлен удельный вес вредных привычек, случаев угроз и насилия в семье, составлен социологический портрет современной женщины. Проведена оценка качества оказания медицинской помощи беременным женщинам в Харьковской области. Для профилактики потерь беременности, заболеваний у новорожденных необходимы меры по повышению мотивации женщины ответственно относиться к собственному здоровью; существует необходимость активного вмешательства со стороны медицинских работников.
Ключевые слова: женщина репродуктивного возраста, медико-социологическое исследование, неблагоприятные факторы для плода и новорожденного.

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SURGERY

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VIEW ON THE QUESTION OF ACUTE ADHESIVE INTESTINAL OBSTRUCTION

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Abstract. *Currently, peritoneal adhesive disease is one of the common diseases in the world, leading to the quick disability of patients and a significant reduction in quality of life. The article is devoted to necessary of analyze of the causes of peritoneal adhesive disease, adverse outcomes of acute adhesive intestinal obstruction examining genetic, immunological, biochemical and morphological features of this group of patients; distinguish anatomical and topographic criteria for the possibility of using technology as a minimally invasive diagnosis and treatment of adhesive disease of the peritoneum; develop an algorithm for diagnosis, new methods of prevention and treatment of surgical adhesive disease of the peritoneum, its complications.*

Key words: *Peritoneal adhesive disease, morphology, complication.*

Peritoneal adhesive disease is one of the common diseases in the world. Recently spread spectrum and volume of surgical interventions a steady rise in the incidence of postoperative development of peritoneal adhesive disease.

In connection with the widespread introduction into surgical practice surgeries on abdominal organs, the relevance problem peritoneal adhesive disease is growing steadily.

Despite intensive development of minimally invasive technologies that have significantly reduced surgical trauma, the number of the nearest and long-term complications caused by adhesion process is not reduced [5].

Abdominal adhesive disease - a serious illness, often occurring in young and working age. Patients must adhere to a strict diet, and frequent exacerbations peritoneal adhesive disease requiring hospitalization ultimately lead to reduced

disability, emotional instability, sexual dysfunction, personality of neuroticism, disability and significant deterioration in quality of life. In typical clinical situations adhesive disease diagnosis does not present any difficulties, and the choice of method of treatment depends on the presence or absence of intestinal obstruction [7, 11].

In 1971 Dederer wrote that "acute intestinal obstruction has earned notoriety very heavy stream, difficult to diagnose and adverse outcomes for the disease" [13] .

In recent decades, a growing understanding of the pathogenesis of acute adhesive intestinal obstruction, develop new ways to diagnose, treat, cure, improved methods of anesthetic management and extracorporeal detoxification [9, 18].

Common operations that cause abdominal adhesive disease - operations on the descending and rectum (25%), followed by appendectomy (15%), gynecologic surgery (14 %) and total colectomy (9%). In general, 76 % of patients developed adhesions after operations performed below the transverse colon, 14% - above the transverse colon, and in 14 % of cases the cause was peritonitis adhesive obstruction. About 1 % of all admissions to hospitals and surgical laparotomy 3% due to adhesive disease of the abdomen and its complications [1, 8, 22].

Frequency of adhesion formation varies from 67 % to 93% after surgical abdominal operations and is nearly 97% after open gynecologic surgery. In modern abdominal surgery problem of postoperative abdominal adhesions not lost its relevance [6, 12].

Acute adhesive intestinal obstruction distinguish the severity and rapid development of the pathophysiological changes in the forms of strangulation, a variety of clinical manifestations and related difficulties in the diagnosis, tactical and technical complexity of the surgical treatment and prevention [10, 19].

Therefore, postoperative mortality in acute adhesive intestinal obstruction is kept at 15% capacity for work is restored only 40 - 50% of patients, and after conservative treatment - at 30 - 35% [20].

Win acute adhesive intestinal obstruction is 87.6 % of the ileus, due to the constantly growing number of operations on the abdominal organs. Thus, surgical complications and diseases caused by adhesions may occur already in the immediate

postoperative period. According to the summary data, the frequency of early adhesive intestinal obstruction varies between 12 % - 27 % of all types of ileus. In pediatric practice, 8 % of newborns who underwent intervention for abdominal organs, subsequently subjected to laparotomy for acute adhesive intestinal obstruction [9, 14].

Today, there are increasing work, noted the negative impact of adhesions in the pelvic area on the reproductive function of young women: 55% of patients the cause of infertility steel spikes in the fallopian tubes and ovaries, formed as a result of chronic pelvic processes. Adhesions on the background of inflammatory diseases of the internal genital organs also leads to chronic pain in the lower abdomen in 68.1 % of patients undergoing phenomenon of salpingooforit [3, 10].

In the United States over the adhesive disease in 2008, there were about 290,000 hospitalizations, and economic costs amounted to about $ 1.5 billion per year [19].

Hospital stay after adhesiolysis performed laparotomy access in urgent procedure averages 20 days. Mortality reaches 7,0-18,0 %, and at an early form of postoperative adhesive obstruction - 19,5-50,0 %. With each subsequent attack of acute adhesive intestinal obstruction ileus recurrence risk increases with increasing [4, 16].

The rapid growth of advanced technologies in minimally invasive surgery, biology, chemistry, pharmacology and other paramedical fields of science and technology make it possible to put into practice new ways and means of prevention, diagnosis and treatment of adhesive disease. Pathogenetic sound direction in the prevention and treatment AADP is the use of various means of preventing adhesion of convergence and injured peritoneal surfaces [2, 23].

Researchers from different countries appealed to the diagnosis and treatment of adhesive disease of the peritoneum using antiadhesive barrier means. The results of their work are contradictory, possibilities of the methods are assessed differently, many issues require further research and discussion. However, most authors note promising application antiadhesive barrier means, laparoscopic and traditional interventions in patients undergoing surgery for abdominal organs [15, 24].

At 11.6 - 38 % of previously operated patients no signs of intestinal obstruction and the only clinical manifestation of the disease are persistent abdominal pain. It is this group of patients are frequent diagnostic errors leading to unnecessary surgical interventions. Patients with abdominal adhesions often long, unsuccessfully treated without a specific diagnosis. Thus, as a rule, the diagnosis appears neurotic syndrome. Report this tactic due to the difficulty of establishing the true cause of pain [17, 21].

Leading role in the diagnosis of peritoneal adhesive disease and X-ray methods of investigation of the gastrointestinal tract. Previously developed technique of X-ray of the stomach, followed by passage of barium and follow-up of his evacuation does not always give an idea about the topic of the process, especially when there vistseroparietal adhesions. Using similar methodology to the background pneumoperitoneum enhanced its diagnostic significance. Further improvement of the method of contrast study was retrograde filling of additional colon double contrast background for the detection of colon pathology. These methods have one very significant drawback - a large radial load and invasiveness studies at low specificity and sensitivity [2, 7, 17].

Ultrasonography (USG) abdomen, widespread in recent years, opening up new possibilities in the diagnosis of peritoneal adhesive disease, especially in the development of acute adhesive intestinal obstruction. However, ultrasound helps to choose the zone entry troacars into the abdominal cavity, free of vistseroparietal adhesions [10, 15, 19].

The role of laparoscopy in the diagnosis of peritoneal adhesive disease is currently not fully understood. According to some authors, the presence of adhesions is a contraindication for laparoscopy and the risk of its use when other methods unjustified. With the advent of new technologies in endoscopic surgery and the development of safe methods of laparoscopic approach in terms of relaxation, as well as with the use of ultrasound to visualize the possibilities of the method vistseroparietal adhesions increased significantly decreased and the number of complications [4, 25].

Development and outcome after surgery reparation paramount depends on the local reaction of inflammatory cells, the state of local immunity, which controls the differentiation of progenitor cells into fibroblasts and regulate their activity. Laws of dysregulation of the immune system in the formation of adhesions remain virtually unexplored.

Lately pathogenetic search methods for prevention and impact on the adhesion process is conducted among drugs acting on immunobiological reactivity of the organism. Set of preventive measures directed only to the activation of immune and cellular elements proliferation by affecting the local inflammation.

Method laparoscopy was first used to treat the adhesive disease and its complications with high efficiency (53 to 80 %) in pediatric surgery [12, 23].

But remains undeveloped algorithm treatment of this disease, as conservative therapy provides only a temporary effect, and in 52.9 % of patients he absent. Traditional surgical interventions used in intestinal obstruction and do not give the desired effect, inevitably causing a recurrence of adhesions. To diagnose the cause of obscure abdominal pain in recent years have increasingly used the laparoscopic approach. Operative laparoscopy is widely used to treat patients with abdominal adhesions disease [10, 13, 18].

Wide-ranging discussion on the diagnosis, surgical treatment of adhesive disease abdomen indicates sustained urgency of this problem. Heterogeneity of symptoms, diagnostic difficulties and ambiguity of interpretation of the results obtained, as well as the inadequacy of existing differential criteria cause difficulty in choosing a rational method of treating a disease. It remains unclear place minimally invasive interventions in the treatment of painful forms of abdominal adhesive disease [4, 7, 12].

In connection with the above stated, we believe it is necessary to analyze the causes of peritoneal adhesive disease, adverse outcomes of acute adhesive intestinal obstruction examining genetic, immunological, biochemical and morphological features of this group of patients; distinguish anatomic and topographic criteria for the possibility of using technology as a minimally invasive diagnosis and treatment of

adhesive disease of the peritoneum; develop an algorithm for diagnosis, new methods of prevention and treatment of surgical adhesive disease of the peritoneum, its complications.

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Резюме. В даний час спайкова хвороба є одним з найбільш поширених захворювань у світі, що призводить до швидкої інвалідизації хворих і значного зниження якості життя. Стаття присвячена необхідності аналізу причин перитонеальної спайкової хвороби, несприятливих результатів гострої спайкової кишкової непрохідності, з дослідженням генетичних, імунологічних, біохімічних і морфологічних особливостей цієї групи хворих. Виділено анатомічні та топографічні критерії для можливого використання технології мінімально інвазивної діагностики та лікування спайкової хвороби очеревини, розробки алгоритму для діагностики, нових методів профілактики і лікування хірургічної спайкової хвороби очеревини, її ускладнень.
Ключові слова: спайкова хвороба, морфологія, ускладнення.

Резюме. В настоящее время спаечная болезнь является одним из наиболее распространенных заболеваний в мире, что приводит к быстрой инвалидизации больных и значительному снижению качества жизни. Статья посвящена необходимости анализа причин перитонеальной спаечной болезни, неблагоприятных исходов острой спаечной кишечной непроходимости, с исследованием генетических, иммунологических, биохимических и морфологических особенностей этой группы больных. Выделены анатомические и топографические критерии для возможного использования технологии минимально инвазивной диагностики и лечения спаечной болезни брюшины, разработки алгоритма для диагностики, новых методов профилактики и лечения хирургической спаечной болезни брюшины, её осложнений.
Ключевые слова: спаечная болезнь, морфология, осложнения.

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DIFFERENTIATED INOTROPIC SUPPORT AS A MEAN OF PROPHYLACTIC OF THE HEPATORENAL SYNDROME IN PATIENTS WITH ABDOMINAL SEPSIS

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***Abstract**. At article, we showed the influence of dopamine and dobutamina on splahnitichny blood flow and their impact on cellular metabolism in patients with abdominal sepsis.*
***Key words:** inotropic support, patients, sepsis.*

Acute liver failure and hepatorenal syndrome (ALFHS) is a key component of multiple organ dysfunction syndrome (MODS) in patients with abdominal sepsis [1].

Experimental and clinical studies provide evidence to suggest that severe systemic vasodilation in conjunction with vasoconstriction of splanhic area and subsequent tissue hypoxia can stimulate gypofiltraion of kidney and fluid retention in parenchymal organs, violation of hepatic blood flow with the development of liver failure [2]. This mechanism is one of the key in the pathogenesis of ALFHS that develops in patients with abdominal sepsis. One of the main ways of preventing and treating this syndrome, along with adequate surgical debridement, antibiotic and fluid therapy - is the use of tools that improve systemic hemodynamic and blood flow splanhnic, but do not have the opposite effect on the kidneys and liver. Traditionally, the most commonly used drug that stimulates the central hemodynamics, improves blood flow and a diuretic effect, as dopamine. Largely thanks to this its properties dopamine routinely used for many years and is used for prevention and treatment of MODS in patients with abdominal sepsis. At the same time, accumulated over the

past years, data indicate the presence of dopamine in cumulative properties and an ambiguous effect on the endocrine profile in critically ill patients [3]. An alternative to it is considered nondopaminerg inotropes - dobutamine [4]. At the same time, the available data in the literature suggest that the restoration of splanhnic blood flow accompanied by postischemic reperfusion syndrome, translocation, which may lead to the generalization of inflammatory mediators, relapse of systemic inflammatory response and the development of MODS [5].

The aim of the present work - to determine the effect of low doses of dopamine and dobutamine in the liver and kidney function and dynamics of cytokine status in patients at risk of ALFHS on the background of abdominal sepsis in the early postoperative period.

Materials and methods.

A prospective, randomized study in 30 male patients with a risk of ALFHS on the background of abdominal sepsis (6-8 points on the scale SOFA). The median age was 50 years. Patients were divided into 2 groups. In group 1 (n = 16) was administered at a dose of dopamine of 200 g / min, at 2 (n = 14) - dobutamine in a dose of 175 mcg / min. The drug is administered during the first three postoperative days.

Studied standard clinical and laboratory parameters septic syndrome, hepatic and renal function (creatinine, bilirubin, ALT serum hourly diuresis), and the content in the blood plasma levels of TNF-α, IL-1 and IL-4. These parameters were studied at 1, 2 and 3 postoperative days. Statistical report - license package Microsoft Exel.

Postoperatively, patients received comparable intensive care according to current protocols, which was unchanged throughout the study.

Results and discussion.

Substantial and statistically significant differences in clinical and laboratory parameters in patients with sepsis syndrome in both groups were observed at all stages of the study, except for indicators of body temperature and leukocytosis (Table. 1).

Table. 1.

The dynamics of clinical and laboratory parameters of septic syndrome

The dynamics of clinical and laboratory parameters of septic syndrome	Group Stages	Performance of the of the study patients		
		1-st day	2- st day	3- st day
The number of respiratory movements, min	1	28±2	24±3	26±3
	2	27±2	23±2	27±3
Heart rate, min	1	110±5	105±3	98±2
	2	108±4	103±4	97±2
Body temperature, C^o	1	38,8±0,15	37,6±0,12*	37,5±0,15
	2	38,7±0,13	37,7±0,11*	37,6±0,15
White blood cell count*10^9	1	18,5±2,1	16,7±1,1	16,5±1,5
	2	18,7±2,2	17,1±1,1	16,7±1,3
Immature forms, %	1	16,5±1,4	12,8±1,4	9,7±1,4*
	2	16,7±1,1	13,1±1,3	11,2±1,2*

All patients had abnormal liver function and kidney failure, which appeared clinic hyperbilirubinemia, increased alanine transferase and creatinine (Table. 2).

Table. 2.

The dynamics of clinical and laboratory parameters hepatorenal functions on the stages of the study

The dynamics of clinical and laboratory parameters hepatorenal functions on the stages of the study	Group Stages	Performance of the study patients		
		1st day	2nd day	3rd day
Bilirubin, mg / dL	1	23,9 ± 0,2	13,8 ± 0,2	13,8±0,2
	2	21,5 ± 0,2	13,9±0,2	13,7±0,2
Alanine transferase/ mmol	1	1,5±0,1	1,3±0,1	1,4±0,1
	2	1,5±0,2	1,4±0,1	1,5±0,1
Creatinine in mg / dL	1	2,7±0,1	2,6±0,1	2,5±0,1
	2	2,6±0,3	2,0±0,2	1,6±0,1**
Diuresis, ml / h	1	55±2	90±4*	115±10**
	2	68±4	74±5	75,7±5

Note: * - p <0.05 compared with the original data,** - P <0.05 for the comparison between groups.

During the research it was found that dopamine stimulated diuresis, but does not change creatinine clearance. Conversely, dobutamine caused a significant increase in creatinine clearance, but without a significant increase in diuresis. Reliable both positive and negative effects on their liver function tests were observed.

Studies have shown that the use of dopamine in the prevention and treatment ALFHS shown in patients with reduced diuresis, while in patients with preserved diuresis, but a reduced filtration capacity, substantiates the use of dobutamine. Question combined their use remains controversial and requires further research.

Background in the study of cytokine was observed a significant increase of concentrations of pro-inflammatory cytokines TNF-α and IL-1 and a decrease in IL-4, anti-inflammatory in both groups, indicating that the development of the phenomenon of reperfusion (Table. 3).

Table 3.

Dynamics of cytokine background on the stages of research

Dynamics of cytokine background on the stages of research	Group Stages	Performance of the study patients		
		1st day	2nd day	3rd day
TNF-α, pg/ml	1	28,5	37,6	50,4*
	2	27,6	38,4	51,2*
IL-1, pg/ml	1	8,2	12,3	12,5
	2	7,9	11,4	12,1
IL-4, pg/ml	1	20,5	8,4	9,2
	2	19,8	7,9	9,1*

Note: * - p <0.05 compared with the original data.

Despite the relative interpretation of these indicators [6], analyzing the results, it can be noted that dopamine and dobutamine causes symptoms of the phenomenon of reperfusion in the form of increasing concentrations of proinflammatory cytokines. At the same time, routine methods of investigation of the dynamics of clinical and laboratory parameters of septic syndrome indicates a decrease in its severity. At the same time, there was no significant positive side of the liver. Given the physiological characteristics of the portal system can assume that one of the important reasons for preserving hepatic dysfunction when restoring blood flow is secondary splanhnitic

cytokine load and reticuloendothelial system. Consequently, one of the main ways of preventing the onset and progression of post-ischemic reperfusion syndrome, translocation can be recovery or, at least, the optimization of the natural barrier function of the intestine.

Conclusion. 1. Patients with primary dopamine acts as a diuretic and improves the creatinine clearance. 2. Dobutamine increases creatinine clearance without significant changes in urine output. 3. Both drugs cause the development of the phenomenon of post-ischemic reperfusion-translocation.

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Резюме. В роботі показано вплив дофамина и добутаміна на сплахнитичний кровотік та їх вплив на клітинний метаболізм у хворих на абдомінальний сепсіс.
Ключові слова: инотропна піддтримка, паціенти, сепсис.

Резюме. В роботе показано влияние дофамина и добутамина на сплахнитичный кровоток и их влияние на клеточный метаболизм у больных с абдоминальным сепсисом.
Ключевые слова: инотропная поддержка, пациенты, сепсис.

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TREATMENT OF PATIENTS WITH BILE LEAKS AFTER LAPAROSCOPIC CHOLECYSTECTOMY

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Abstract. *The analysis of treatment of 216 patients with bile leaks after laparoscopic cholecystectomy is done. In 56 patients bile leakage ceased on the background of conservative therapy, 22 patients had intra-abdominal bile collections, which required draining operations, most of them were performed by miniinvasive approaches. Endoscopic papillotomy was performed in 73 patients, in 29 with removal of stones, endoscopic stenting of common bile duct – in 14 patients. 47 patients underwent reconstructive surgery for common bile duct injuries. Minimally invasive interventions take a leading place in the treatment of postoperative bile leaks, but open surgery have not lost their importance in a number of indications.*
Key words*: laparoscopic cholecystectomy, bile leak, common bile duct injury*

Bile leaks after laparoscopic cholecystectomy (LCE) is one of the most common postoperative complications [1]. Its clinical significance ranges from self-controlled bile leaks to life-threatening early (bile peritonitis, sepsis) and late (biliary strictures) conditions. The most often sources of bile leaks after LCE are: gallbladder bed, cystic stump and common bile duct injury (CBDI) [2]. Conditions that predispose to bile leaks include obstruction of distal common bile duct, obscure anatomy and all risk factors of CBDI. Preoperative diagnosis of patency of the distal common bile duct remains a pressing problem of biliary surgery. On average, 10% of patients with chronic cholecystitis, and 15% of patients with acute cholecystitis have choledocholithiasis. With the introduction of laparoscopic cholecystectomy (LCE), the patients are operated on earlier for gallstone disease (GSD), which reduced the incidence of choledocholithiasis in the western countries to 5%. Unfortunately, a thorough medical history, physical examination, biochemical blood tests (total

bilirubin, transaminases, amylase, lipase), ultrasonography (USG) of the abdominal cavity is not always possible to detect a violation of patency of the distal common bile duct before the cholecystectomy and avoid CBDI. In addition, a number of patients are operated in emergency procedures when there is no way to do all necessary tests.

Aim: To develop a program of treatment of patients with bile leaks after LCE.

Materials and Methods. Results of treatment of 216 patients treated in the Institute of General and Urgent Surgery of AMSU in 2005-2013 is presented. Most patients (112) were transferred after primary operations in other hospitals of the city of Kharkiv and Kharkiv region. These patients were admitted in a period from 3 days to 4 weeks from the initial surgery. The rest 104 patients underwent LCE in Institute. There were 168 females and 48 males. Age ranged from 21 to 84 years. Patients were examined by routine clinical and laboratory tests, ultrasound, CT, ERCP fistulography.

Results. The primary intervention in all patients was LCE with subhepatic drainage. Bile leak volume ranged from 100 ml to 1000 ml per day, the last corresponded to the total external biliary fistula. The phenomena of jaundice occurred in 15 patients accompanied with cholangitis in 8. 22 patients had intra-abdominal bile collections, in 12 with signs of diffuse bile peritonitis. Following a comprehensive clinical-laboratory and instrumental examinations aimed at assessing the general condition of the patient, the presence of intra-abdominal complications, the presence of the common bile duct obstruction, further tactics was determined.

The primary goal was the resolution of intraabdominal complications caused by bile leaks. Thus bilomas were drained under ultrasound guidance in 6 patients, relaparoscopy, drainage of the abdominal cavity was performed in 14, laparotomy, choledocholithotomy, common bile duct drainage, drainage of the abdominal cavity was performed in 2. 3 patients from this group required further interventions to control bile leak after external drainage.

The next goal was to determine the cause of bile leaks. Patients with low-grade bile leaks without local and general complications undergo conservative treatment,

which was effective in 56 cases (in these patients the cause of bile leaks remain obscure). The remaining patients together with 3 patients that were drained for intraabdominal bile collections underwent diagnostic tests (ERCP and/or fistulography). The sources of bile leak were: gallbladder bed – 11 patients, cystic stump – 22, CBDI – 73, in the rest cases the source was not identified. ERCP diagnosed residual choledocholithiasis in 35 patients, stenosis of the distal common bile duct due to chronic pancreatitis – in 18, stenosis of major duodenal papilla – in 20, CBDI without obstruction of common bile duct – in 61. In 7 patients ERCP was not possible due to technical reasons (Billroth-II gastrectomy, a large parapapillar diverticulum).

The main treatment for these patients was endoscopic. Endoscopic papillotomy was performed in 73 patients, common bile duct stone removal – in 29 patients. These interventions have proved effective in 98 (90.7%). Among the complications acute pancreatitis was observed in 14 patients, of whom two with severe pancreatitis, bleeding from papilla incision – in 2, which was controlled conservatively. There were no deaths. 7 patients in whom ERCP was not possible and another 10 patients who failed endoscopic treatment underwent laparotomy, drainage of common bile duct. 57 patients had CBDI without obstruction of distal portion of common bile duct. Endoscopic stenting was successful in 14 patients. The rest 47 patients underwent open interventions for CBDI: repair of CBDI on T-drain or transhepatic drain in 7 cases; Rough-en-Y hepaticojejunoanastomosis in 40 patients. There were two deaths. One patient with biliary peritonitis died due to multiple organ failure, other patient died due to cardiac failure on the second postoperative day after Rough-en-Y hepaticojejunoanastomosis.

Discussion. Bile leaks are rather frequent complication after gallbladder removal. Despite the fact that the manifestation of this condition is characterized by the bile discharge from the abdominal cavity, its causes and severity varies widely [1]. It may be self-controlled within 5-7 days bile leak, as well as life-threatening condition with the development of bile peritonitis or persistent external biliary fistula due to CBDI. All bile leaks are characterized by a particular source, which can be

both intrahepatic and extrahepatic biliary ducts, and therefore the problem is often discussed in the section of the LCE threatening complications like CBDI. The frequency of this complication in the literature varies widely, and about its treatment there are divergent points of view [2].

The first line tactical approach in patients with bile leaks after the LCE is the identification of possible intra-abdominal complications (biliary peritonitis, intraabdominal bile collections). For this purpose, thorough clinical assessment together with diagnostic investigations (ultrasound and CT) is used. In presence of the intra-abdominal bile collections minimally invasive techniques (drainage under ultrasound guidance and relaparoscopy) were used. We prefer to perform relaparoscopy in early period after LCE (14 cases) and percutaneous drainage under US-guidance in more late terms (6 cases). Only in cases of diffuse bile peritonitis we perform laparotomy, external biliary drainage, drainage of the abdominal cavity (2 patients). In the absence of intra-abdominal complications conservative tactic is used initially. In other cases, measures, aimed to identify both the source and cause of bile leak, are performed.

Carefully analyzing the clinical cases of bile leaks we noted the following anatomical, technical and clinical predictors of this complication. Leak from cystic duct stump develops usually for two reasons or their combination: on the one hand, it is difficult cystic duct stump closure (wide cystic duct, the presence of a small stones, severe inflammatory changes in the cystic duct), on the other hand the presence of bile hypertension in biliary tree (choledocholithiasis, constrictive papillitis, stenosis of the distal portion of common bile duct, acute pancreatitis).

Injury of the bile ducts in the gallbladder bed occurred in the traumatic separation of the gallbladder wall from the liver (especially in sclerosed gallbladder, when the wall of the gallbladder is intimately fixed to the liver parenchyma), or in the presence of aberrant duct in gallbladder bed.

The most dangerous cause of bile leak is CBDI. Its causes are listed in detail in numerous papers and most accurately are described by the triad: dangerous anatomy, dangerous pathology and dangerous surgery. In these patients, the elective tactics is

used depending on the type and level of injury, presence of jaundice or intra-abdominal complications. Minimally invasive approaches (endoscopic stenting) if possible is first line approach during the last decade [3, 4]. However, open surgical procedures do not loss their significance. They are considered in the following situations: 1) the inability to perform ERCP (gastrectomy after Billroth-II, contraindications), 2) the ineffectiveness of endoscopic interventions, and 3) major CBDI. It is very important to determine the optimal time to perform repeated surgery. In the presence of common bile duct drainage definite surgery can be postponed until a month later, which favors remitting inflammatory changes in the area of intervention and recovery of the patient.

Conclusions. The current trends of treatment of bile leaks after LCE are focused on the use of minimally invasive techniques. This is primarily endoscopic papillotomy, endoscopic stone removal if present and stenting. In addition, minimally invasive draining interventions (under ultrasound control, laparoscopic) should be used for intraabdominal bile collections. Open procedures are indicated for diffuse biliary peritonitis, major CBDI when ERCP is not possible or contraindicated.

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Резюме. У роботі проведений аналіз лікування 216 пацієнтів з жовчевитіканням після лапароскопічної холецистектомії. У 56 хворих витікання жовчі припинилось на тлі проведення консервативної терапії, 22 пацієнти мали інтраабдомінальні скупчення жовчі, що вимагало дренуючих операцій, більшість з яких виконано мініінвазивно. Ендоскопічна папілосфінктеротомія виконана 73 пацієнтам, у 29 з видаленням конкрементів, ендоскопічне стентування гепатикохоледоху – у 14. 47 пацієнтам проведені відновні і реконструктивні операції з приводу пошкоджень жовчних протоків. Малоінвазивні втручання мають провідне значення у лікуванні післяопераційних жовчевитікань, однак відкриті операції не втратили свого значення при низці показань.
Ключові слова: лапароскопічна холецистектомія, жовчевитікання, пошкодження жовчних протоків

Резюме. В работе проведен анализ лечения 216 пациентов с желчеистечениями после лапароскопической холецистэктомии. У 56 больных истечение желчи прекратилось на фоне проведения консервативной терапии, у 22 пациентов отмечены интраабдоминальные скопления желчи, что требовало дренирующих операций, большинство из которых выполнено миниинвазивно. Эндоскопическая папиллосфинктеротомия выполнена 73 пациентам, у 29 с удалением конкрементов, эндоскопическое стентирование гепатикохоледоха - у 14. 47 пациентам проведены восстановительные и реконструктивные операции по поводу повреждений желчных протоков. Малоинвазивные вмешательства имеют ведущее значение в лечении послеоперационных желчеистечений, однако открытые операции не утратили своего значения при ряде показаний.
Ключевые слова: лапароскопическая холецистэктомия, желчеистечение, повреждение желчных протоков

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THE QUESTIONS OF A CHRONIC PANCREATITIS PATHOGENESIS AND ITS COMPLICATIONS

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Abstract. *Biochemical studies were performed in 47 patients with pancreatic pseudocysts, aged 4.,58 ± 7.38 years, male / female ratio of 8.4: 1. All patients were operated on. Studies have shown that the level of IL-18 was higher in patients with type I pseudocysts 1.9 times with type II - 1.2 times and type III - 1.3 times compared with the control. Such a tendency was noted for IL-6 and IL-8 against increase of IL-10 in a 27.4-fold, respectively (I pancreatic pseudocysts type), 28.1 times (II pancreatic pseudocysts type) and 21.4 fold with III type of pancreatic pseudocysts. The content of IL-18 and glutathione peroxidase in blood in different types of pancreatic pseudocysts directly correlates with the severity of pancreatitis. We found a close correlation between the level of IL-18 and glutathione content in blood at an unfavorable prognosis of postoperative period.*

All patients had development of endothelial dysfunction and endothelial damage, as svidetestvovalo a significant increase in plasma VEGF respectively 176.4% (I type pseudocysts), 129.2% (II type pseudocysts) and 54.2% (III type pseudocysts) relative to the control. These data suggest that this creates favorable conditions for the remodeling of the pancreas when the defect replaced cloth with lower levels of the organization, such as scar and repeated cell injury leads to greater activation of PSCs and increased production of extracellular matrix components.

Keywords: *pancreatic pseudocyst, matrix metaloproteinaze pathogenesis.*

The chronic pancreatitis (CP) concerns to group of chronic diseases of a pancreas (P), mainly inflammatory causes, with phase-progressing focal, segmentary or diffuse degenerate and its destructive changes of exocrine part, an atrophy of glandular elements (pancreacytes) and replacement by their fibrous tissue; changes in ducts system of P; cysts and calculus formation; different degree disorder of exocrine and endocrine functions. CP is polyetiologic disease of P which develops owing to attacks of acute pancreatitis (AP) or traumas of P. As for literatures testify, prevalence CP nearly 30 cases on 100 000 persons [1]. Priority directions of modern researches in pancreatology understand the mechanism of loss functioning of P tissue

and replacement by its connective tissue. The development of fibrous changes of P, as consequence of the dynamic cascade of cytokine, chemokine, factors of growth and many other factors, balance infringements between processes of synthesis and disintegration proteins of extra cellular matrix (ECM) with its accumulation and degradation [2]. Pancreafibrosis now it is considered as the leading pathological mechanism of development CP and its complications, and main role in this process perform pancreatic stellate cells (PSCs) [3, 4].

The hypothesis formulated by us became a basis for research carrying out that in hypoxia and ischemia conditions of P after its damage, angiogenic factors support endotheliocytes activation and proliferation, which comes to the end with processes neovascularization, and insufficient degradation of extracellular matrix is the cause of progressive fibrosis and remodulating P with development of complications. Thus we considered that re modulating of P is heterogeneous process which leads to changes in a connecting fabric and infringement of structure and function of P.

The work purpose – to define profibergenic mediators, markers of endothelial dysfunction and hemostasis at patients with different types complications of pancreas pseudocysts.

Materials and research methods. The investigation is approved by Ethical committee. The participants have been completely informed. Researches was done at 47 patients in age average (43,58 ± 7,38) years, a parity of the man / women 4:1.

Criteria of inclusion: pseudocysts of P on classification A. D'Egidio and M Schein: to I type are carried postnecrotic pseudocysts of P, which were formed after episode of acute pancreatitis or traumas of P; to II type – postnecrotic pseudocysts of P, which were formed owing to attacks of AP at patients with CP; to III type – retention cysts which arose after CP as a result of pancreas channels stricture [4].

Criteria of cutting off: in our research did not include patients with a liver pathology (hepatitis, cirrhosis, cancer) and cancer of P, the secondary arterial hypertension, accompanying endocrine, autoimmune, oncology pathology, with the expressed infringements of a warm rhythm and conductivity, with acute heart attack,

acute heart insufficiency, cardiomyopathy, accompanying mental diseases, narcotism, alcoholism.

All patients have been divided into three groups: the first – patients with I type pseudocysts of P, complicated by suppuration (12) and acute bleeding in a cavity of cyst (2); the second – patients with II type pseudocysts of P (12 – suppuration, 3 – bleeding in a cavity of cyst, 1 – rupture of cyst with a bleeding in abdomen cavity); the third – III type pseudocysts of P (17 patients the fibrous-degenerate pancreatitis complicated by development by secondary portal hypertension, mechanical jaundice, etc. Groups of patients were comparable ($\chi 2=1,234$, $p>0,05$).

Clinical investigation included estimation of complaints, gathering of the anamnesis of the basic disease and accompanying pathology, an estimation of anthropometrical indicators (height, weight, an index of weight of a body), electrocardiogram, definition of the basic clinical and biochemical parameters of the blood and urine, ultrasonic, CT, MRT, radiographic examination of stomach and intestine. Was done an estimation of inflammation factors, hypoxia and conditions of fabric reconstruction of P. Defined VEGF, MMP-9, it inhibitor TIMP-2 and a complex with inhibitor (MMP-9/TIMP-2 in serum blood with use immune-enzyme method: IL-6, MMP-9, TIMP-2 research by commercial diagnostic sets of firms R&D Diagnostics Inc. (USA): Human MMP-9 Quantikine ELISA Kit, category DMP900; Human TIMP-2 Quantikine ELISA Kit, category DTM200 <http://www.rndsystems.com/Products/DTM200>); Human IL-6 Quantikine ELISA Kit category D6050; Human TGF-beta 1 Quantikine ELISA Kit category DB100B. Definition of plasmatic level IL-8, IL-18 and IL-10 was carry out by immune-enzyme method and test systems manufacture «Bender Medsystems» (Austria). Glutathione peroxidase (GPO) blood activity investigated on spectrophotometer. A method principle: GPO (1.11.1.9) catalyzes oxidation reaction of restored glutathione in presence of a cymene substrate which is an oxidizer. Activity of enzyme defines on decrease of substratum G-SH in color reaction on hydrosulfide groups with Elman

reactant [5]. Malonic dialdehyde (MDA) in blood serum defined by spectrophotometric method on L.I. Andreevoj and co-authors (1988).

Statistical processing of results was carry out by software package "Biostatistics" (Russia). The correlation analysis applied to an estimation of communication of two quantitative values and was carrying out by Spearmen method and the one-factorial dispersive analysis.

Results and their discussion. Clinical displays and the laboratory characteristic are resulted in tab. 1. At 22 (46,8 %) patients hyperthermia was observed, at 16 (34 %) – jaundice, at 9 (19,1 %) – disturbance of duodenal patency, at 8 (17 %) – disturbance P and at 4 (8,5 %) – wirsungolithiasis, at 14 (29,8 %) – regional portal block. Complications are noted at all patients: pseudocyst of P suppuration at 100 % of the first group, obstruction jaundice at 23,5 % of the second and 57,1 % of the third group; disturbance of duodenal patency 7,1 % of patients of the second and 26,7 % – the third group; calcification of P at 24 % patients of the third group; wirsungolithiasis at 14,3 % patients of the third group; regional portal block at 14,3 % patients of the second and 21,4 % – the third group; compression of adjacent organs – at 42,9 % patients of the second group; association of different complications – at 28,6 % patients of the second and third group.

The basic concept of optimum complex of patients treatment which we use since 90th years old of last century, the maximum preservation of functional P reserve, which is based on use of four basic directions at all stages is: 1) the control of abdomen pain; 2) the treatment of maldigestion syndrome; 3) "management" of complications; 4) as it is possible preservation of organs parenchyma at surgical interventions on P. All patients have been operated. At I type pseudocyst of P have been used puncture drainage interventions under ultrasonic control (10 patients) and open operative interventions with external drainage of pseudocyst cavities and biological tamponade by omentum with external drainages, (4 patients). At II type pseudocysts of P have been executed – drainages interventions under control by ultrasonic (14), and at 2 patients – operative interventions with tamponade cyst cavities in as a result of bleeding in a cavity. Patients III type pseudocyst of P after

preliminary punctures under ultrasonic control was done resection of ventral parts of head of P by Frey (11 patients), a subtotal resection of head of P by Bern modification (3 patients) and cystodigestiv drainage (3 patients). From 47 analyzed patients has died 1 from arrosion bleeding.

Table 1.

The clinical- laboratory characteristic of patients with pseudocyst of P
(Me (Q1-Q3))

Indicator / control	Groups of patients		
	The first (n=14)	The second (n=16)	The third (n=17)
Age	43,6 (26-55)	45,4 (34-59)	44,2 (32-57)
M/F	12/2	12/4	14/3
Body masses index, kg/m^2	24 (21-28)	23 (21-26)	21 (20-26)
Blood leukocytes, × 10^9/l, 6,23 (5,2-8,5)	14,8 (12,1-18,7)*	9,7 (5,5-11,9)* **	8,2 (5,9-10,8)*
Blood amylase, gr/h×l, 17,3 (14,5-24,7)	64,6 (60,2-73,8)*	48,7 (24,7-62,1)* **	24,8 (21,1-28,9)* ***
General protein, g/l, 75,6 (65,9-81,3)	63,1 (60,2-67,8)*	64,5 (63,3-69,4)*	65,2 (60,7-73,2)*
General bilirubin, mkmol/l 10,44 (9,1-16,2)	22,4 (14,8-34,2)*	27,2 (17,1-42,2)* **	44,8 (40,6-64,5)* ***
Alaninaminotransferaise, ME×l, 27,8 (12,4-37,8)	82,4 (36,7-94,8)*	45,2 (40,2-57,3)* **	44,8 (39,9-52,7)* ***
Aspartataminotransferaise ME×l, 29,44(14,2-35,6)	95,4 (87,8-102,1)*	97,2 (91,2-112,3)*	96,5 (92,4-105,6)*
Blood glucose, mmol/l 5,13 (4,1-5,9)	7,2 (5,6-12,4)*	9,2 8,7-14,3)*	7,4 (7,1-12,3)*
Blood creatinin, mkmol/l 71,7 (64,2-98,4)	85,5 (78,1-115,3)*	89,5 (81,3-93,8)*	77,9 (62,6-89,7)* ***
IL-18, pg/ml 235,7 (213,4-267,8)	438,4 (363,01-488,7)*	292,06 (256,45-305,2)*	299,7 (247,6-324,7)*
IL-10, pg/ml 3,2 (0-8,6)	87,59 (64,97-111,7)*	89,76 (55,61-98,9)*	68,36 (33,37-85,2)*
IL-18/ IL-10 3,7 (0-31,1)	5 (5,6-4,4)	3,3 (4,6-3,1)	4,4 (7,4-3,8)
IL-6, pg/ml 34,5 (2,1-45,3)	347,7 (214,5-424,2)*	238,4 (193,5-367,3)* **	214,6 (145,7-254,3)*
IL-8, pg/ml 15,6 (3,8-22,1)	198,6 (178,2-212,4)*	99,02 (86,3-123,5)* **	87,8 (66,5-102,5)*
MDA, mkmol/l 2,11 (2,04-2,24)	5,04 (4,77-5,34)*	4,05 (3,45-5,1)* **	2,87 (2,45-3,11)* **
GPO, mkkat/g x Hb, 6,12 (5,89-6,22)	9,7 (8,91-12,1)	11,25 (8,67-13,6)	13,75 (12,1-16,8)

The note: * – it is authentic with control; ** – it is authentic between 1 and 2 groups; *** – it is authentic between 2 and 3 groups (p <0,05).

Substantial increases of enzymes activity of LFT were observed at patients with different types of pseudocysts of P. As testify cited given (tab. 1), level of IL-18 was above in the first group of patients in 1,9 times, in the second – in 1,2 times and in the third – in 1,3 times in comparison with control ($p < 0,05$). The tendency is noted for IL-6 and IL-8 against increase IL-10 accordingly in 27,4 times (I type pseudocyst of P), in 28,1 times (II type pseudocyst of P) and in 21,4 times at III type pseudocyst of P. The possible increase in level IL-10 is attempted to reduce production pro-inflammatory cytokines which continues to last.

At the same time, level anti-inflammatory cytokines at patients III type pseudocyst of P on the average on 22 % was more low, than at patients with I type pseudocyst and on 26,1 % – than at patients with II type. IL-18, also known as the factor inducing IFN - γ (IGIF). It has initially been characterized as potential inductor synthesis IFN - γ T - and NK- cells.

IL-10, derivative Tx2, it can be considered as the antagonist of some the cytokines. So, IL-10 suppresses production IFN γ Th1. Besides, it brakes proliferative answer of T- cells to antigens and mitogens, and also suppresses secretion activated monocytes IL-1β, IL-6 and TNF. At the same time IL-10 stimulates secretion Ig B- cells. IL-10 also can stimulate synthesis Ig E that conducts to development of hypersensitivity of immediate type. In the influence on cellular immunity IL-10 has synergistic action with IL-4. At various pathological conditions increase of level IL-10, this increasing is bad prognostic sign. IL-10, powerful transforming grossing factor (TGF) b, regulate a regeneration phase, reduces fibrosis and atrophy.

Detailed studying of cytokines effect can be base for working out of medicines for treatment of acute and chronic pancreatitis [6]. So, by us it has been established that maintenance IL-18 and glutamic phase (GF) in blood serum, at various types pseudocysts of P, directly correlates with condition patients, and simultaneous decrease GF and increase IL-18 in comparison with indicators which were registered the day before, on 30 % and is more connected with the bad prognosis ($r = - 0,87$, p

<0,01). In our opinion, it testifies to deep depression of antioxidant protection, an exhaustion of its reserves as result of lipid peroxidation activation and oxidant stress. Modern researches have proved, that the pancreatitis is initiated as an inflammation condition, destruction of acinar and ducts cells, intra – and perilobular fibrosis and sclerosis parenchyma of P. According to experts, necrosis, apoptosis and fibrosis are dynamic processes and accompanied by polypeptide control which concerns TGF-b1, one of which functions is balance regulation between the negative and positive processes occurring in P tissue [7]. At experimental researches it has been established that hyper production TGF-b1 promotes induction at animals as pancreatitis, and an accompanying TGF-a-diabetes [8]. TGF-b1 activates pancreatic stellate cells and strengthens them synthesis of extracellular matrix (ECM), including collagen I and III types. This cytokine inhibit degradation of (ECM) at the cost of specific metalloenzyme activity decrease [9]. TGF-β1, which is key profibrosis cytokine, has been significantly raised at patients of all groups. Pseudocysts of P accordingly on 1807,5 %, 521,9 % and on 412,2 % in comparison with control group that, obviously, testifies to one of roles conducting it in development intra – and perilobular fibrosis irrespective of the trigger mechanism of pancreatitis development and its complications. However the maximum increase TGF-β1 nevertheless was observed in group of patients with acute pseudocysts of P, were formed after 4-6 weeks from beginning of AP.

It is established that definition circulating TGF-β1 can display various stages of a current of a pancreatitis and expressiveness of complications which develop in various terms from the disease moment. The obtained data will be coordinated with opinion of authors [5, 6, 9, 10, 11], which have proved that the transforming factor of growth β1 (TGF-β1) – is predictor which influences the processes of proliferation fibroblasts initiation, synthesis of components ECM, cooperation cells of an inflammation (first of all macrophages). In experimental works on animals the high expression of TGF-β1 in acute phase of an inflammation and in a late stage of fibrosis is defined, and influence on immune system effects TGF-β 1, with inhibit functions prevailed. TGF-β1 stimulates structure PZH change, it remodeling, has

important role in development fibrosis and potentiating apoptosis cells of P. This morphological reorganization can be a basis of pancreatitis pathogenesis.

It is known, that IL-6 is one of the most active cytokines, participating in inflammatory reaction. In researches which we have spent, level IL-6 has appeared considerably raised in all groups of patients with pseudocysts of P in comparison with control. In case of TGF-β1 level research in blood, increase IL-6 was maximum at patients with I type pseudocysts of P, that will be coordinated with researches which discuss the status of cytokine as an ischemia biomarker [12, 13]. At all types pseudocysts of P the level of gelatinize B increased in relation to control group (fig. 1). At patients with I type pseudocysts of P the level of MMP-9 was raised on 73,5 %, at II type – on 64,7 % and at III type - on 45,5 % accordingly (p <0,001). Concentration of the inhibitor matrix metalloproteinase (TIMP-2), was on the average on 51,6 % above at patients with I type pseudocysts of P, than at control group (p <0,001); at patients with II type of distinction were doubtful; at patients about III type – level TIMP-2 was an average on 9,6 % more low, than an indicator in control group (p <0,05) (fig. 2).

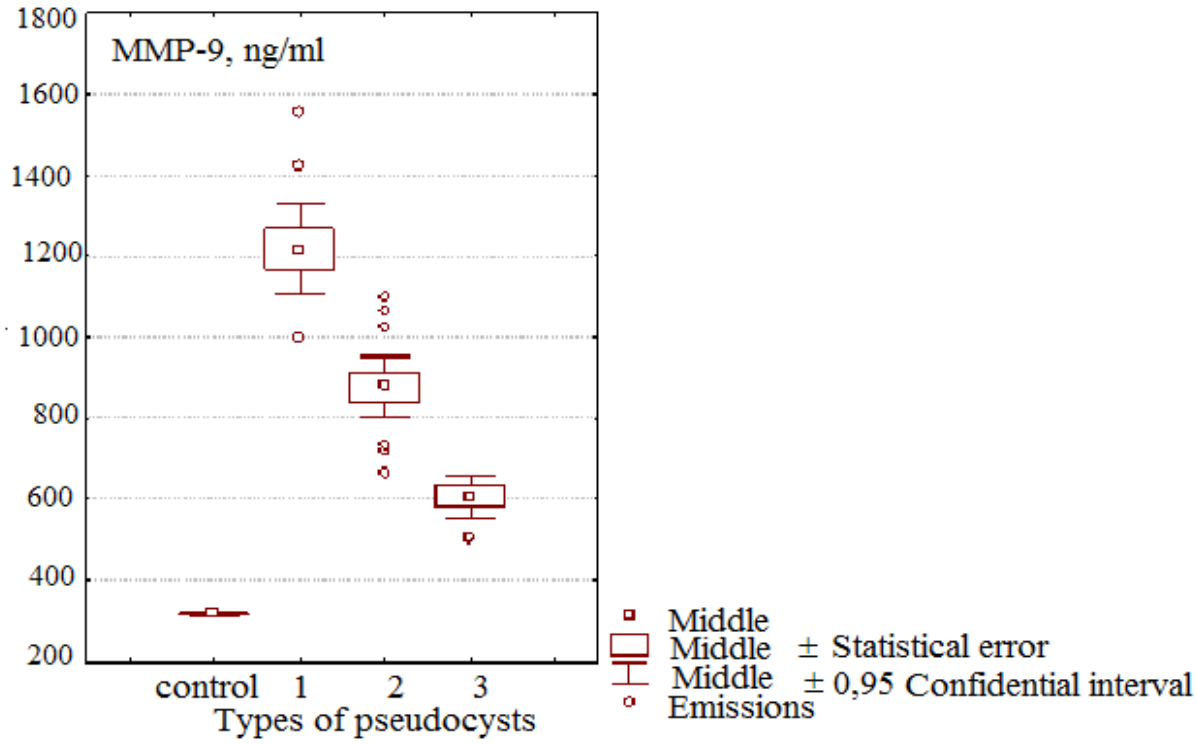

Fig. 1. Maintenance MMP-9 in a blood at patients with pseudocysts of pancreas

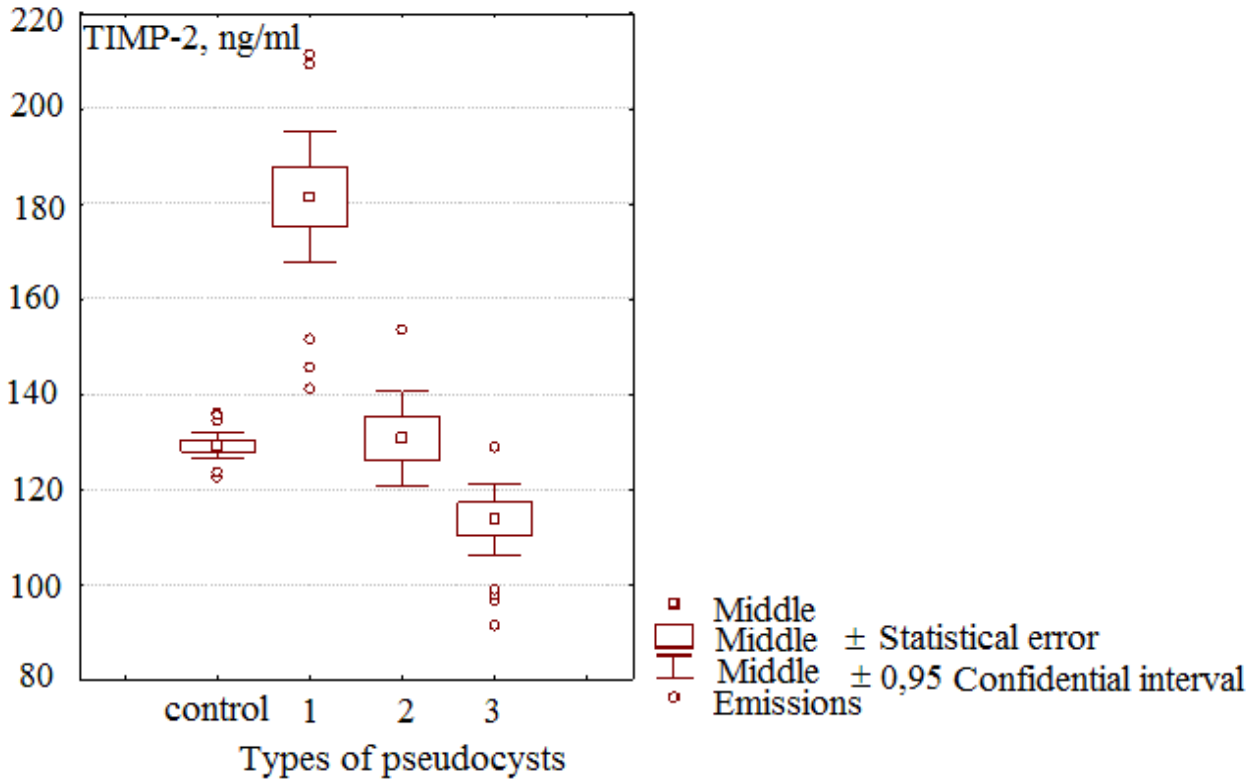

Fig. 2. Maintenance TIMP-2 in a blood at patients with pseudocysts of pancreas

Coefficient of MMP-9/TIMP-2 (coefficient of MMP-9 inhibition) was above at patients with I and II types pseudocysts of P, and has made accordingly 6,3 and 7,1 (in control group – 2,45) ($p < 0,001$). At patients with III type pseudocysts the inhibition factor on MMP-9 was more low, than in first two groups, but on 109,8 % exceeded indicators of control group ($p < 0,001$). Parity MMP-9 / TIMP-2 was above at patients of 2nd group and on 189,8 % exceeded indicators of control group, on 12,7 % – indicators which have been fixed in 1st group of patients and on 38,1 % – indicators which have been fixed in 3rd group of patients ($p < 0,05$) (fig. 3).

It is known that in the course of the development pseudocysts of P during the early period (the first 4-6 weeks from the beginning of acute pancreatitis), there passes a number of stages: 1) accurately prospective progressing inflammatory infiltrate 2) acute congestion of a liquid; 3) formation encapsulate congestions of the liquid with amylase and limited by fibrous tissue of peritoneum. Absence of epithelium allows differentiating pseudocyst and new cysts. Among the basic components which produce activated PSCs is collagen of I type and in smaller

quantities collagens of III and IV types, and also fibronectin, laminin, hyaluronic acid, etc.

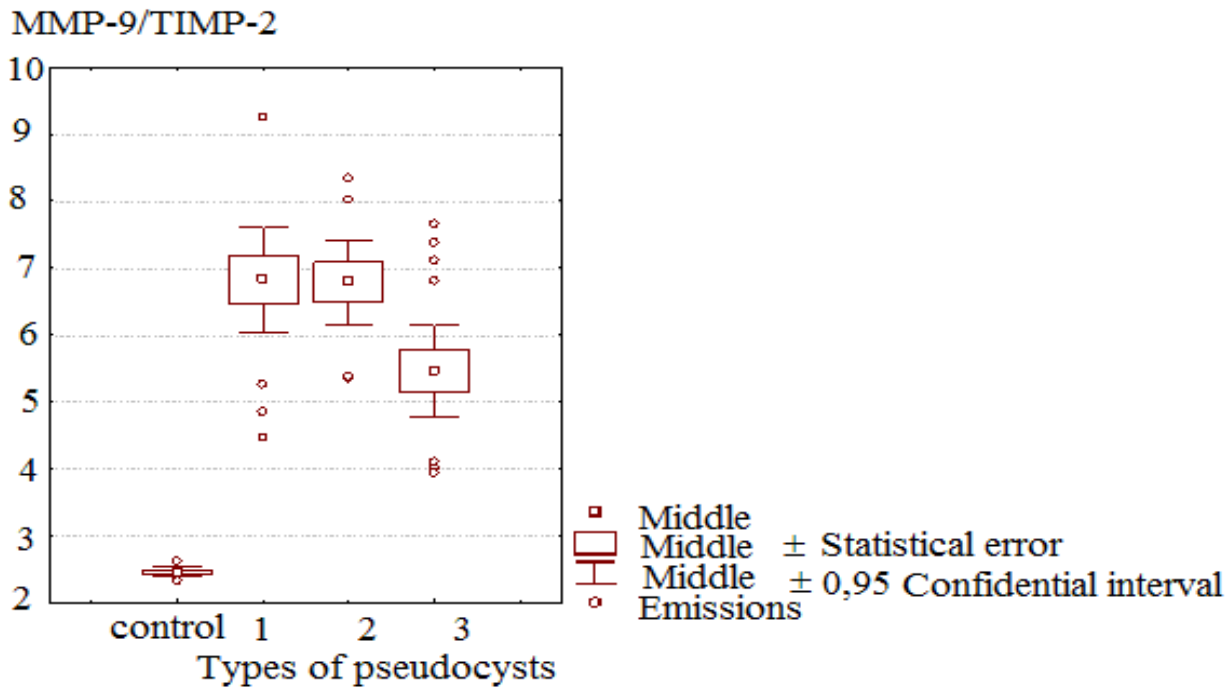

Fig. 3. Inhibition factors on MMP-9 at patients with different types pseudocysts of pancreas

For disintegration ECM answer metalloproteinase matrix – as endopeptidase group, which are made PSCs, and them proteolytic activity is regulated by tissue inhibitors – protein group, which the same produced by PSCs. Expression regulation of metalloproteinase occurs at three levels: 1) by genome; 2) by activation of proenzymes and 3) by inhibition of enzymes activity with the assistance of tissue inhibitors. Modulators of expression of MMP are TNF-a, IL-1b, IL-8, IL-17, epidermal growth factor (EGF), transforming factor of growth (TGF), etc. All of them cause proof functions disturbance of various types of immunocompetent cells [14]. Osteocalcitonin, doxycycline, retinoids, glycosaminoglycans to inhibit by expression of MMP.

The expression of MMP is name the major factor in development of degradation ECM, "critical step" in it remodeling, the marker of inflammation activity, of fibrosis and sclerosis of P. Hyaluronic acid, tissue inhibitors MMP

(TIMP-1, 2), laminin, leptin, collagen of IV type, etc. are used as the indicators reflecting quantity of a connective tissue [15].

Activity of enzymes depends as on level of an expression of their genes, and presence of activators and inhibitors. MMP, basically, concern to "induced" enzymes which transcription submits to variety factors: steroid and thyroid hormones, cytokines, growth factors, chemical agents, etc. The exception makes MMP-2 which expression occurs on constitutional type, and regulation of activity of enzymes at post transmitting level is carried out by activation of zymogens or interaction with tissue inhibitors MMP [16, 17].

Contribution of PSCs to pathology of P is not limited to superfluous production of a connecting tissue, but also they stimulate growth factors, transforming factor (TGF-b), platelet (PDGF), etc. Besides, the bacterial infection and endocellular production of oxygen radicals [18] promote formation strengthening P fibrosis. Proliferation PSCs leads to formation of new blood vessels. These processes grow out of development P hypoxia and actions vasoactive mediators and cytokines: nitrogen oxide and other factors [19]. The process of angiogenesis is necessary for long adaptation of tissue in the conditions of damage, and the main mechanism of regulation of processes angiogenesis vasoactive is liberation of angiogenic factors.

Angiogenesis can be induced by processes an increase of concentration of stimulators and decrease level of inhibitors, or a combination of those and other processes. Thus, the essence of angiogenesis processes consists that after expansion of vessels and increase of their permeability occurs compression of endothelial cells and reduction of density of intercellular contacts. At pathological processes angiogenesis amplifies that can influence on the processes in ECM [20].

Vasculoendothelial growth factor (VEGF) – potential mitogen for epithelial cells of vessels. It strongly influences permeability of vessels, is powerful angiogenic tissue, participates in processes neovascularity at various pathological situations, is studied last years, including CP. Thus, the conducted researches have shown that the aggressive and heavy current at patients with pseudocysts of P (8 and more points on scale SOFA) associates with presence of higher values of level MMP-9, and

progressing fibrosis and development of complications in patients III type of pseudocysts associates with inhibition of TIMP-2. Thus the average level of a studied indicator, was not only more low, than at patients of the first and second groups, but also on the average on 9,3 % was below indicators of control group ($p < 0,05$). We had been spent studying of intragroup correlation communications between VEGF (indicator of hypoxia and damages of endothelium), MMP-9 and TIMP-2 to blood of patients with pseudocysts of P (tab. 2). The conducted researches have shown, that in at all types pseudocysts of P there was a positive communication only between level MMP-9 and VEGF: at I type it has made 0, 57 ($p <0,05$); at II type – 0,76 ($p <0,05$); at III type – 0,68 ($p <0,01$). Results of research show that at all patients development endothelium dysfunctions with damage of endothelium to what substantial increase in plasma of blood VEGF accordingly on 176,4 % (1 group), 129,2 % (2 group) and on 54,2 % (3 group) in relation to control ($p <0,05$ testified) was observed.

Thus, by means of the single-factor dispersive analysis it is possible to estimate the importance of distinctions between average values of indicators in four groups. Apparently from resulted data, at confidential probability of 0,95 % ($p <0,05$) indicator MMP-9 significantly differs in all four groups. For TIMP-2 distinctions are observed only for the first and third groups of patients as among themselves, and in relation to control and to the second group. Average relations of MMP-9 / TIMP-2 are significantly various only for control group and the third group among themselves and in comparison with the first and second groups. High activity of MMP-9 and TIMP-2 at patients with I and II types pseudocysts of P, probably, is caused by compensatory reaction, directed on suppression destruction of collagenic network (basically - collagen IV) and on the prevention further reorganization of connecting tissue of P. At progressing fibrosis of P (the third group of patients) MMP-9 and TIMP-2 decreased in comparison with the first and second groups of patients. At III type pseudocysts of P the level of gelatinize was on 83,6 % above indicators of control group, but on 51,4 % and on 35,1 % more low, than at patients with I and II types pseudocysts of P. Thus average level TIMP-2 accordingly on 40,4 % and 11 % ($p <0,05$) in the third group of patients was more low, than in the first and second

groups. It is known that MMP-9 is the induced enzyme which transcription depends on variety of factors: level of cytokines, factors of growth, chemical agents etc., and this enzyme plays an important role at chronic phases of various illnesses [21].

Table 2

Intragroup correlation communications between levels VEGF, MMP-9 and TIMP-2 at patients with pseudocysts of pancreas

I type of pseudocysts of pancreas			
	VEGF	MMP-9	TIMP-2
VEGF	**1,0000**	0,57, p<0,05	0,09, p>0,05
MMP-9	0,57, p<0,05	**1,0000**	–0,23, p>0,05
TIMP-2	– 0,23, p>0,05	0,09, p>0,05	**1,0000**
II type of pseudocysts of pancreas			
	VEGF	MMP-9	TIMP-2
VEGF	**1,0000**	0,76, p<0,05	0,25, p>0,05
MMP-9	0,76, p<0,05	**1,0000**	0,24, p>0,05
TIMP-2	0,25, p>0,05	0,24, p>0,05	**1,0000**
III type of pseudocysts of pancreas			
	VEGF	MMP-9	TIMP-2
VEGF	**1,0000**	0,68, p<0,01	0,07, p>0,05
MMP-9	0,68, p<0,01	**1,0000**	0,3, p>0,05
TIMP-2	0,07, p>0,05	0,24, p>0,05	**1,0000**

The regress of extracellular matrix occurs also because of apoptosis of PSCs. Further all depends on, whether action of the harmful factor (viruses, autoantibody, toxins, etc.) stops. If the pathogenic factor stop it works, there is collagen degradation. Such variant is favorable and similar supervision are described at patients with a syndrome of overload by iron and copper, alcohol-induced liver defeat, chronic virus hepatitises after virus elimination, hepatitis etc. [21]. These researches allow us to assume that in conditions of hypoxia and ischemia of P, as a

result of its damage by, angiogenic factors there is an activation and proliferation of endotheliocytes, which comes to the end by remodeling of vessels and neovascularization processes. Owing to infringements of balance between synthesis of proteins and their disintegration the structure pancreocytes of P is changes. Delay of processes of recycling of extracellular matrix components, which collects in a zone of damage of P, conducts to delay of a reparation processes and can be main cause of fibrosis with development of CP and its complications, including – as a result of repeated influence of factors exogenous and endogenous nature and activation PSCs, about what can increases in concentration TIMP-2 and increases of factors of inhibition MMP-9 at all types pseudocysts of P. Accordingly it creates favorable conditions for remodeling of P when, defect of organ parenchyma is replaced with a tissue, for example – scar, and repeated damage of cells conducts to bigger activation PSCs, that promotes formation of CP and its complications.

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Резюме. Проведено біохімічні дослідження у 47 хворих з псевдокістами підшлункової залози, у віці 43,58 ± 7,38 року, співвідношення чоловіки /жінки 8,4:1. Хворих було розподілено на три групи згідно класифікації псевдокіст підшлункової залози за A. D'Egidio та M. Schein (1991). Всі хворі були оперовані. Резекцію вентральної частини голівки ПЗ за Фреєм виконано у 11 пацієнтів, субтотальну резекцію голівки ПЗ за Бернською методикою – 3, дренування порожнини кісти – у 14 (у поєднанні з протоковою системою ПЗ – у 3), пункційно-дренуючі втручанні під контролем УЗД – у 10, відкриті

оперативні втручання та зовнішнє дренування порожнини псевдокісти – у 4 хворих. З 47 пацієнтів, що аналізуються, помер 1 від арозивної кровотечі. Проведене дослідження підтвердило, що рівень IL-18 був вищим у хворих на I тип псевдокіст в 1,9 рази, на II тип – в 1,2 рази і на III тип – в 1,3 рази у порівнянні із контролем ($p<0,05$). Подібна тенденція відзначена й для IL-6 та IL-8 на тлі підвищення IL-10 відповідно в 27,4 рази (I тип псевдокіст ПЗ), в 28,1 рази (II тип псевдокіст ПЗ) та в 21,4 рази при III типі псевдокіст ПЗ. Встановлено, що вміст IL-18 і глутатіонпероксидази в сироватці крові при різних типах псевдокіст підшлункової залози безпосередньо корелює з тяжкістю панкреатиту. Нами виявлено тісну кореляцію між рівнем IL-18 і змістом глутатіонпероксидази в крові при несприятливому прогнозі перебігу після операційного періоду: $r= – 0,87$, $p<0,01$

Дослідженнями підтверджена висока активність ММП-9 та ТІМП-2 у хворих на I та II типи псевдокіст ПЗ, що, можливо, зумовлено компенсаторною реакцією, яка направлена на пригнічення деструкції колагенової мережі (переважно – колагену IV) та попередження подальшої перебудови сполучної тканини ПЗ. При прогресуванні фіброзу ПЗ (третя група хворих) ММП-9 та ТІМП-2 знижувались у порівнянні з першою та другою групами хворих. При III типі псевдокіст ПЗ рівень ММП-9 був на 83,6% вище показників контрольної групи, але на 51,4% та на 35,1% нижчим, ніж у хворих на I та II типи псевдокіст ПЗ. При цьому середній рівень TIMP-2 відповідно на 40,4% та 11% ($p<0,05$) в третій групі хворих був нижчим, ніж в першій та другій групах. У всіх хворих спостерігався розвиток ендотеліальної дисфункції з пошкодженням ендотелію, про що свідчило значне підвищення у плазмі крові VEGF відповідно на 176,4% (I тип псевдокіст), 129,2% (II тип псевдокіст) та на 54,2% (III тип псевдокіст) по відношенню до контролю ($p<0,05$). Отримані дані дозволяють припустити, що це створює сприятливі умови для ремоделювання підшлункової залози, коли дефект парехими заміщується тканиною з нижчим рівнем організації, наприклад – рубцем, а повторне ушкодження клітин веде до ще більшої активації PSCs і збільшення продукції компонента позаклітинної матриці.

Ключові слова: псевдокісти підшлункової залози, матриксні металопротеїнази, патогенез.

Резюме. Проведены биохимические исследования у 47 больных с псевдокистами поджелудочной железы, в возрасте 43,58 ± 7,38 лет, соотношение мужчины/женщины 8,4:1. Больные были разделены на три группы согласно классификации псевдокист поджелудочной железы по A. D'Egidio и M. Schein (1991). Все больные были оперированы. Резекция вентральной части головки ПЖ по Фрею выполнена 11 больным, субтотальная резекция головки ПЖ по Бернской методике – 3, дренирование полости кисты – у 14 (в сочетании с протоковой системой ПЖ – у 3), пункционно-дренирующие вмешательства под контролем УЗИ – у 10, открытые оперативные вмешательства и наружное

дренирование полости псевдокисты – у 4 больных. С 47 анализируемых больных, умер 1 от аррозивного кровотечения.

Проведенные исследования доказали, что уровень IL-18 был выше у больных с I типом псевдокист в 1,9 раза, со II типом – в 1,2 раза и с III типом – в 1,3 раза по сравнению с контролем ($p<0,05$). Подобная тенденция отмечена и для IL-6 и IL-8 на фоне повышения IL-10 соответственно в 27,4 раза (I тип псевдокист ПЖ), в 28,1 раза (II тип псевдокист ПЖ) и в 21,4 раза при III типе псевдокист ПЖ. Установлено, что содержание IL-18 и глутатионпероксидазы в сироватке крови при разных типах псевдокист поджелудочной железы непосредственно коррелирует с тяжестью панкреатита. Нами выявлена тесная корреляция между уровнем IL-18 и содержанием глутатионпероксидазы в крови при неблагоприятном прогнозе течения послеоперационного периода: $r= – 0,87$, $p<0,01$

Исследованиями подтверждена высокая активность ММП-9 и ТИМП-2 у больных с I и II типом псевдокист ПЖ, что, возможно, обусловлено компенсаторной реакцией, которая направлена на угнетение деструкции коллагеновой сети (преимущественно – коллагена IV) и предупреждения дальнейшей перестройки соединительной ткани ПЖ. При прогрессировании фиброза ПЖ (третья группа больных) ММП-9 и ТИМП-2 снижалась по сравнению с первой и второй группами больных. При III типе псевдокист ПЖ уровень ММП-9 был на 83,6% выше показателей контрольной группы, но на 51,4% и на 35,1% ниже, чем у больных с I и II типом псевдокист ПЖ. При этом средний уровень ТИМП-2 соответственно на 40,4% и 11% ($p<0,05$) в третьей группе больных был ниже, чем в первой и второй группах.

У всех больных наблюдалось развитие эндотелиальной дисфункции с повреждением эндотелия, о чем свидетествовало значительное повышение в плазме крови VEGF соответственно на 176,4% (I тип псевдокист), 129,2% (II тип псевдокист) и на 54,2% (III тип псевдокист) по отношению к контролю ($p<0,05$). Полученные данные позволяют предположить, что это создает благоприятные условия для ремоделирования поджелудочной железы, когда дефект парехимы замещается тканью с более низким уровнем организации, например – рубцом, а повторное повреждение клеток приводит к еще большей активации PSCs и увеличению продукции компонента внеклеточного матрикса.

Ключевые слова: псевдокисты поджелудочной железы, матриксные металопротеиназы, патогенез.

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CONSCIENCE-BASED MEDICINE: NEW APPROACHES TO THE MANAGEMENT OF PROSTATE CANCER PATIENTS

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Time to focus on patients not profit. Emphasize medicine not money … be a patient care specialty … ethics based on what is best for the patient … service to community.
R. G. Evens, 1989

…the absolute necessity for medical leadership to recognize the need for change; establish common professional values; create a vision; and provide courage, strength, and passion to make the correct strategic choices to empower the success of medicine in the future.
R. W. Holden, 1998

Abstract. *Almost half of prostate men cancer, the disease is benign and not life threatening. However, some patients with aggressive tumors have manifestations that can lead to death if not treated. Now the problem concerns to predict the nature of its course. This will prevent useless severe treatment when most patients the tumor can be controlled minimal therapeutic intervention or even just to keep the patient under regular diagnostic control. At present there are real possibilities to confidently enough differentiate the cases where a radical medical aid to the patient is needed and where either only minimal therapeutic support or even just regular periodic examinations and consultations would suffice. What is respectfully acknowledged at major meetings and in editorials is not being applied to patients. The explanations are complex and rooted in a conflict between knowledge and belief with disturbing undertones of economic self-interest. It is time to practice conscience-based medicine.*
Keywords*: prostate cancer, management of patients, conscience-based medicine.*

Prostate cancer (PC) is one of the most common men cancer. In North America early expected number of new prostate cancer cases ranges from 219,000 to 240,000 cases and from 27,000 to 31,000 deaths [1-4]. As one of the five or six men will

develop PC at some point in their lives. Incidence increases with age — more than 65% of cases are diagnosed in men of 65 and older [5, 3].

Moreover, 50% of men older than 50 years at autopsy have PC, but the probability of clinical diagnosis is only about 18%. The estimated probability of dying from PC for men is set at 2.8%, while the most common actual cause of death of men diagnosed with PC are cardiovascular diseases [6, 7]. In another autopsy study it was showed that highly differentiated prostatic intraepithelial neoplasia, which is the precursor of PC, is present in almost 86% of men aged 80 years and older [8]. In 30-50% of men who are diagnosed with PC, the disease is benign and not life threatening [9].

However, some patients with aggressive tumors have manifestations that can lead to death if not treated. Hence, early detection of aggressive forms of the disease helps to reduce mortality in the treatment of localized disease and is the only chance for successful treatment [10, 11]. Before the broad distribution of early PC detection methods, including digital rectal examination and transrectal ultrasound studies and measurements of serum PSA, in most cases PC was diagnosed in the stage of progression of the disease and the men died within a few years after diagnosis.

So now the problem concerns not only accurate diagnosis of PC, but more importantly, to predict the nature of its course. This will prevent useless severe treatment when most patients the tumor can be controlled minimal therapeutic intervention or even just to keep the patient under regular diagnostic control, which should be guaranteed by using effective methods.

R. Choo et al. [12] and L. Klotz [13] propose to determine the decision to intervene by PSA kinetics and/or histological progression of the tumor. This strategy offers the attraction of individualizing therapy based on the biological behavior of cancer. Paients with slow growing tumor will be spared the negative effects of radical treatment, while patients with rapidly progressing cancer will benefit from this therapy.

Many options for the management of patients with newly diagnosed PC are availble. Magnetic resonance imaging (MRI) plays an important role in the early

diagnosis of PC. Moreover, it helps identify the remains of the tumor after surgery or relapse after treatment, when there is clinical or biochemical suspicion of it. The feasibility to assess PC using conventional MRI, T1-and T2-weighted sequences, MR spectroscopy, diffusion-weighted imaging, and dynamic contrast enhancement MRI has been investigated. All forms of treatment to a greater or lesser extent alter the MRI features of the prostate, and it is important to be able to distinguish between the effects of treatment and recurrent or residual cancer to aid in further clinical patient management [14].

Doubts exist with respect to the benefits of a broad screening for PC. In a recently published European study has shown that screening for PC may provide a reduction in mortality from this cancer by 20%, but to avoid one death 48 patients should be radically treated [15]. This study emphasizes that although screening and early detection provide benefits in terms of reducing mortality, yet they create a significant risk of unnecessary treatment. This is a dilemma that underlies the requirement of selective treatment approach. Estimates show that 50% of men who have PC diagnosed on the basis of screening would not have any clinical symptoms of PC during their lifetime [16]. To avoid excessive treatment of patients with not an aggressive tumor, life expectancy and clinical manifestations, such as tumor stage, PSA level, and biopsy Gleason should be taken into account [9]. Currently, histopathological analysis of biopsy material obtained by transrectal ultrasonography in check is performed on a Gleason scale. This leads to an underestimation of the aggressiveness of the tumor in 26%-41% of biopsy samples compared with samples obtained at prostatectomy [17-20].

There is evidence that screening for PC by PSA serum levels reduces mortality from this disease, but this has a side effect — a high level of false-positive diagnoses. The fraction of false-positives ranged from 3.3 to 12.1% in one round, and 12.5% of men had at least one false positive result for three rounds [21]. Also indicated is that digital rectal examination, transrectal ultrasound and PSA are limited as screening tests due to-their lack of sensitivity, specificity and in efficiency costs [11, 22, 23]. PC, hyperplasia, and prostate inflammation are characterized by varying degrees of

elevated PSA levels [24-26]. The growth rate in serum PSA during the year before diagnosis (PSA speed), as shown in a number of researches, is significantly associated with the time of recurrence, cancer-specific mortality [27-29], and external beam radiotherapy [30]. In addition, conventional ultrasound, which is used for biopsy guidance, i snot accurate enough for biopsy even in the Doppler mode [31]. Contrast-enhanced transrectal ultrasound is more sensitive for the detection of malignant cells in the prostate without significant loss of specificity [32].

Researched were CT signs such as uneven edge of the prostate and obliteration of the angle between the prostate and neighboring seminal vesicles. It became apparent that CT data is neither sufficiently sensitive nor specific for the detection of tumor sprouting, compared to what is needed for making therapeutic decisions. MRI definitely has better contrast and spatial resolution than CT [33]. Many comparisons of MRI features and pathological findings are published, and the literature contains a number of MRI features for detection of extra capsular distribution tumors [34-42].

In a large study, E. Kuligowska et al. [43] determined the accuracy of PC detection by means of: (a) gray and color Doppler transrectal ultrasound, (b) excessive levels of PSA in blood serum, and (c) six fold transrectal biopsy under ultrasound control. There also was a relationship between angiogenesis in the tumor and biological activity of the tumor assessed by means of ultrasound data. Gray scale ultrasound images found 41.1% of cancer cases, while color Doppler ultrasound imaging revealed additional 15.8% (56.9% total) cases. By using biopsy 56.8% of cancer cases were found, while a six fold biopsy revealed 43.2% more cancer cases (100% total). Tumor hypervascularization that was determined by color Doppler ultrasonography correlates with biological aggressiveness of tumors. PSA level was normal in 30.5% of patients with PC. The authors concluded that gray scale transrectal ultrasound even in combination with color Doppler ultrasound is insufficient for PC screening, so biopsy should always be accompanied by a selection of six biopsy samples.

Anatomical and metabolic prostate mapping with MR spectroscopy make it possible to optimize treatment planning (expectant management, surgery, or

radiotherapy- intensity-modulated or brachytherapy), and, therefore, to further expand the role of MRI in achieving a truly individual approach to the patient management [44].

M. McNaughton-Collins et al. [11] studied the effect of pelvic irradiation on the serum PSA. Patients received irradiation at a total dose of 50.4 Gy or more (1.8 Gy per fraction) and 25.0 Gy with fractions of 5.0 Gy. Rapid rise in PSA level was found during the first 3 weeks (up to 3.7-fold increase compared to the initial). At the end of treatment PSA level was almost no different from the initial, and later declined to 77%.

Thus, it can be noted that at present there are real possibilities to confidently enough differentiate the cases where a radical medical aid to the patient is needed and where either only minimal therapeutic support or even just regular periodic examinations and consultations would suffice. Methods of the disease treatment vary widely from observation without intervention to a very aggressive surgery or radiation therapy, which is currently available in several variants. There is much debate regarding the best or most acceptable treatment for different stages of the disease.

Management options are numerous. A recent study of the primary treatment received by 11,892 men with newly diagnosed PC showed that in approximately 7% of cases active surveillance was elected, 50% — radical prostatectomy, 12% — external beam radiation therapy (RT), 13% — brachytherapy, 4% — cryoablation, and 14% — androgen deprivation therapy [45]. Other treatments, such as high-intensity focused ultrasound and photodynamic therapy are also becoming increasingly available. Continuous improvement and refinancing of these treatment strategies, along with the trend towards early detection and reduction in PC stage at diagnosis led to a 99% relative survival at 5 years after diagnosis [5]. However, some patients showed recurrence of the tumor, which is often suspected based on digital rectal examination or PSA levels increase. MRI may play an important role in the evaluation of these patients. The choice of treatment depends on several factors, including the probability of accurate diagnosis of PC, the degree of histological

aggressiveness of the tumor, the age and overall health, including co-morbidities, as well as the expected results and possible side effects associated with different forms of treatment [46-48].

The optimal treatment for men with PC remains controversial for several reasons. First, the possibility of setting an accurate diagnosis, so that imaging cannot always identify metastatic PC. Second, the Gleason grade, which is one of the most important factors predicting disease progression, is subjective and depends on the interpretation of the present biopsy material by pathologist [49]. Third, screening for PC based on PSA is not always certain. Fourth, an important consideration in the choice of treatments given is the quality of life [50, 51]. Finally, given that most patients with PC are men of advanced age, aging population makes it important to carefully examine the results of treatment, so that they can have a very significant impact on the overall health of the population. In this sense, the use of large databases is extremely valuable and powerful resource for epidemiological studies because the general population is more heterogeneous compared with hospitals or centers of observational studies [52].

L.M. Franks [6] evaluated the results of a waiting strategy with selective delayed intervention and using the definition of PSA progression or histological signs as indications for early treatment of clinically localized PC. Active surveillance for localized PC of low degree of aggressiveness may reduce the risk of over-treatment of clinically insignificant tumors, while preserving the possibility of definitive therapy for those patients who are transferred over time into the category of high risk.

There are several treatment options for localized PC: radical prostatectomy, brachytherapy, external beam radiation therapy, androgen deprivation therapy and active surveillance [52-55]. E. H. Zhou et al. [52] studied the relationship between disease specific survival and the four standard methods of treatment (radical prostatectomy, brachytherapy, external beam radiotherapy, androgen therapy) and observation without treatment within 6 months after the diagnosis of PC. The study included 10,179 men aged 65 years and older with prostate cancer cases diagnosed between 1999 and 2001, and the follow up to 2005. Treatments were clinically

acceptable treatment options for the disease. It was shown in this population-based study that radical prostatectomy and brachytherapy is associated with improved survival of patients.

One of the standard treatments for locally advanced disease is a radical course of external beam radiotherapy combined with androgenic suppression. Large multi center randomized trials in Europe [56] and North America [57] showed a high level of disease-free survival when using this approach.

Brachytherapy alone or combined with external beam radiotherapy has been widely recognized as a first line treatment for patients with localized prostate cancer [58-60].

N. Pervez, et al. [61] studied the acute toxicity of intensity modulated radiation therapy combined with androgen deprivationin patients with high risk PC. The total local dose was 68 Gy in 25 fractions (2.72 Gy/fraction) for 5 weeks. Irradiated were prostate and seminal vesicles. Simultaneously, pelvic lymph nodes received 45 Gy in 25 fractions. For the treatment of patients a tomotherapy unit with intensity modulation was used. Manifestations of acute toxicity were recorded weekly during treatment and in 3 months at the end. Maximum acute toxicity was as follows: 35% of patients had grade 2 toxicity of the gastrointestinal tract, 6.67% of patients had grade 3 and 33.33% grade 2 of the genitourinary toxicity. Three months after radiotherapy (RT) the toxicity significantly decreased. Therefore, the investigated mode of combined hormonal and radiation therapy is well tolerated.

C. R. King a. D. S. Kapp [62] consider, that after radical prostatectomy the actual doses radical irradiation of prostate bed for both adjuvant radiotherapy (ART) and salvage radiotherapy (SRT) have to be in the range of 60–70 Gy. Greater doses would potentially achieve significantly greater disease-free tumor control rates. ART is radiotherapy which is performed in the immediate postoperative setting, and SRT is performed after a demonstrated in any way (e.g., biochemical) recurrence. ART and SRT offer the potential for radical treatment after unsuccessful prostatectomy (PE). Two randomized studies have demonstrated an improvement in disease-free survival for ART after PE in patients at high risk, defined as pT3 or positive surgical

margin [63, 64]. The positive role of SRT with biochemical relapse after PE has also been demonstrated in numerous studies [66, 67]. In two studies of ART, the total dose to the tumor bed was 60 Gy [64] and 60-64 Gy [65]. For SRT the American Society of Therapeutic Radiology and Oncology has consensus to recommend high doses of radiation, at least 64 Gy in the normal fractionation [68]. There is ample evidence to support dose escalation to 78 Gy for radical RT in localized prostate tumors [69-73].

However, the results of the many studies have shown that acute rectal reaction depends on the dose and the degree of manifestations is also linked. Postoperative RT leads to more acute manifestations of gastrointestinal toxicity than radical RT alone. For postoperative RT it is wise to use various restrictions in dose [74].

RT and RPE are widely accepted treatments for clinically localized prostate cancer. Although these methods have comparable results, a large number of patients who choose RP eventually pass RT [75, 76] either in the adjuvant or salvage form. Depending on the pathological results (e.g., extra capsular penetration, seminal vesicles invasion, positive surgical edges) patients undergoing initial primary RPE may need ART with or without hormone therapy. ART is often administered after RPE to patients with high risk (e.g., extra capsular penetration, seminal vesicles invasion, positive surgical edge, high pT or high Gleason grade) and as has been shown to reduce the risk for metastasis and biochemical recurrence in men with positive the pathological results of the RPE [76]. In addition, patients who initially had RPE then may be subjected to SRT through sustainable growth PSA as biochemical sign of recurrence. The question of whether the RT should be performed immediately or postpone on term for improving the PSA remains controversial [76, 77]. The choice between these treatments (RT with or without hormone therapy, primary RPE plus ART) is largely dependent on their adverse effects and benefits for the patient.

Common side effects of normal tissue as complication of RT include lesions of the rectum and/or bladder. Both acute and late lesions of the gastrointestinal tract and urogenital system after high dose RT were documented. Since toxicity may

eventually become more significant, acute toxicity is an important predictor of late toxicity. Since toxicity may eventually become more significant, acute toxicity is an important predictor of late toxicity [78–82]. Acute side effects can be very serious and lead to interruption of the planned treatment in 10% of patients [83].

Permanent brachytherapy with I-125 and Pd-103 implants at high biologically effective dose of 200 Gy gives 96.9% local control of PC [84]. One of the important benefits of permanent implantation of radioactive grains in the tumor is a very conformal high dose of irradiation to the prostate gland. High doses, as it shown above, are necessary for malignant tumor eradication and significantly reduce the likelihood of biochemical (level PSA) recurrence of the tumor [85, 86]. Therefore various brachytherapy schemes are often used to control tumors in all stages. The results of treatment are usually evaluated by means of biochemical control [87]. The problem of using PSA as an endpoint of a positive treatment outcome is that it does not distinguish between those patients with a systemic recurrence compared to local. In the past, digital rectal examination was used to assess local control. Currently accepted is that prostate biopsy is the best method for determining residual or recurrent local disease [85].

In an editorial in the "Journal of clinical oncology" Anthony Zietman [88] from Harvard Medical School wrote: «What began as a small crack in the solid concept of early detection and early treatment for prostate cancer has now widened and spread. Despite imperfections which limit their interpretation, the recently published randomized screening trials show there is only a small — or even no — improvement in survival from early detection over the first 10 years [15, 89]. One trial also showed that the number of patients (around 50) that must be treated to save one life is alarmingly high [89]. These data come at a time when medical spending, long recognized to be beyond the nation’s means, is to be tightened and restructured along evidence-based guidelines with care being directed preferentially toward areas of proven benefit. The Institute of Medicine has drawn up national priorities for comparative effectiveness research, and the management of localized prostate cancer sits squarely in the first quartile [90]. Indeed, it is the top-ranking oncologic priority.

A perfect storm of clinical evidence and economic reality has arisen in which urologists and radiation oncologists need to examine the evidence, examine their souls, and start to carefully look at every new patient asking, before anything else — is treatment really needed at all? If it is not, and that will frequently be the answer, then they must be prepared to lead the patient along the less financially rewarding and decidedly unglamorous path of active surveillance. The training of resident doctors has to date been so focused on cure, and the culture of early detection/early treatment so deeply ingrained, that it is little wonder that this shift in thinking is yet to reflect itself in everyday practice. What is respectfully acknowledged at major meetings and in editorials is not, in the daily reality of the clinic, being applied to patients. Indeed, in the United States, the proportion of men being managed conservatively has actually been declining [92]. The explanations, as hinted, are complex and rooted in a conflict between knowledge and belief with disturbing undertones of economic self-interest. It is time to practice conscience-based medicine.

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Реферат. Майже у половини хворих на рак простати, хвороба протікає доброякісно і не загрожує життю. Але у деяких пацієнтів пухлини бувають з агресивними проявами і можуть призвести до смерті,якщо не лікуються. Таким чином, наразі ставиться проблема прогнозувати характер її перебігу. Це дасть можливість запобігти марного тяжкого лікування у випадках, коли у більшості хворих пухлину можна контролювати мінімальним терапевтичним втручанням або навіть вести хворого лише під регулярним діагностичним контролем. Наразі існують реальні можливості достатньо впевнено диференціювати випадки захворювання, коли не обхідна радикальна лікувальна допомога хворому від тих, що потребують або мінімальну терапевтичну підтримку, або ж лише регулярний періодичний огляд і консультацію. Але те, що з повагою визнано на великих нарадах та в редакційних статтях, не стало повсякденною клінічною реальністю. Поясненняє складним і йде корінням у конфлікт між знанням і вірою з тривожним відтінком економічних інтересів. Настав час медицини, заснованої на сумлінні.
Ключові слова: рак простати, ведення хворого, сумлінна медицина

Реферат. Примерно у половины заболевших раком простаты болезнь протекает доброкачественно и не угрожает жизни. Но у некоторых пациентов опухоль имеет агрессивное течение и может привести к смерти, если не лечить. Следовательно, ныне проблема состоит в прогнозировании характера заболевания. Это дает возможность избежать для большинства больных тяжкого лечения, контролируя опухоль только минимальными средствами, или даже ведя больного лишь под регулярным активным наблюдением. Ныне существуют возможности достаточно уверенно дифференцировать случаи заболевания, когда действительно не обходима радикальная лечебная помощь больному, от тех, когда нужна минимальная терапевтическая поддержка или даже всего лишь регулярное периодическое обследование и консультации. Тем не менее, то, что признано на широких совещаниях специалистов и в редакционных статьях, не стало широкой клинической реальностью. Найти объяснение этому явлению сложно, и уходит оно корнями, вероятно, в конфликт между знанием и верой с тревожным оттенком экономических интересов. Пришло время медицины совести.

Ключевые слова: рак простаты, ведение больного, основанная на совести медицина.

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REGULATION OF THE UVEOSCLERAL OUTFLOW IN THEPATIENTS WITH PRIMARY OPEN-ANGLE GLAUCOMA

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Abstract. Background. *The aim of our study was to investigate the role of visual load levels in the IOP elevation in the patients taking prostaglandin analogues and to try to optimize the conditions for their effects on the uveoscleral outflow.*
Material and Methods. *33 patients (40 eyes) with first diagnosed primary open-angle glaucoma and resistance to latanoprost 0,005 % intraocular pressure were included in this study. These patients were pre-examined with the definition of visual and reading acuity, refraction, true, tolerant and target IOP with perimetry and ophthalmoscopy. Subjects were divided into 2 groups of comparable age, sex, refraction. In each group the thickness of the ciliary body by ultrasound biomicroscopy was investigated, level of near visual load and tolerated correction for near were defined.*
Results*. It was found, that in both groups 85% of the eyes with POAG had moderately high (3-6 hours per day) and high (more than 6 hours a day) near visual load. Maximal ciliary body thickness in both groups was significantly higher than the results received by other authors: 0.881±0.039 mm in group 1 and 0.889±0.049 mm in group 2. Also a direct dependence of the ciliary body thickness and the true value of intraocular pressure(r=0.52) was observed. The hypercorrection of presbyopia was made in group 1 gradually, in steps of 0.25diopters.The value of additional correctionaveraged0.5 ± 0.13diopters. The magnitude of additional correction was inversely related toage (r=0.79).To assess the effectiveness of presbyopia overcorrection in reducing IOP one year later tonometry, the checking of visual acuity, perimetry (MD/year method), ophthalmoscopy, the thickness of the ciliary body were estimated.In the group 1the reduction of intraocular pressure (17.3 ± 0.84 mm Hg) was statistically significant (p <0.01), its value was close to the average tolerant IOP (17.0 ± 0.67 mm Hg), but was higher than the target (14.3 ± 0.67 mm*

Hg). Also in this group statistically significant (p <0.01) decrease in the thickness of the ciliary body was observed, more marked in patients with high near visual load (r = 0.47). Progression of glaucoma according to perimetry was significantly less (p <0.01) in the group with a hypercorrection of presbyopia as compared with group with ordinary correction.

Conclusions.*Overcorrection of presbyopia, as a way to regulate IOP may be in addition to antihypertensive therapy for patients with high near visual load and POAG.*

Key words: *primary open-angle glaucoma, resistant intraocular pressure, near visual load levels, presbyopia correction, maximal ciliary body thickness.*

Glaucoma is the second leading cause of blindness and the first cause of irreversible blindness worldwide [1].Glaucoma is sensitive to intraocular pressure (IOP)optic neuropathy that produces characteristic structural changes to the optic nerve head, often with correlating the visual field defects [2]. It is a chronic disease, in which the control of intraocular pressure (IOP) is the only evidence-based method of treatment [3-5]. Medical therapy is usually the first line of treatment for POAG, with treatment directed to reaching and maintaining a preestablished “target pressure range” that is expected to stop an optic nerve damage and visual field loss [3,6-8]. The first line medicines are prostamide analogues and beta-adrenergic antagonists. In general, beta-adrenergic antagonists and carbonic anhydrase inhibitors decrease the production of aqueous humour. Prostaglandin and prostamide analogues, which primarily increase uveoscleral outflow, while cholinergics increase trabecular outflow. Finally, alpha$_2$-adrenergic agents both decrease aqueous production and increase uveoscleral outflow [2]. When one particular drug does not help the patient to reach the target pressure level, physicians can change it to a different class medicine or add an another drug from a different class. However, combination with drugs which reduce the production of intraocular fluid and the level of eye hemodynamics can lead to poor nutrition of the anterior eye segment. It can cause premature aging of the anterior eye segment structures with cataract development and so on. Besides cholinergic drugs usage is inappropriate after 40-45 years old due to

age-related decrease of sclera elasticity [9].Furthermore monotherapy with prostaglandin analogues needs to create the optimal conditions for their impact. According to I.N. Koshits et al[10]such conditions occur at a sufficient width of ciliary muscle intralaminar spaces in the state of intermediate (not maximal) contraction. When the tension of ciliary muscle is maximal or its fiber hypertrophy occurs, uveoscleral outflow decreases significantly. The relaxation of the ciliary muscle leads to not maximal state of outflow [10,11]. The aim of our study was to investigate the role of visual load levels in the IOP elevation in the patients taking prostaglandin analogues and to try to optimize the conditions for their effects on the uveoscleral outflow.

Material and Methods. Patient selection was performed in the outpatient department of the Kharkiv Regional Clinical Hospital among the patients with first diagnosed primary open-angle glaucoma, for whom latanoprost 0.005% was prescribed as antihypertensive therapy. These patients were pre-examined with the definition of visual and reading acuity, refraction, true, tolerant and target IOP with perimetry and ophthalmoscopy. For visual acuity estimation decimal notation was used, the table with optotypes was shown to patients at the distance of 5 m. Refraction was determined by autorefractometry and spherical equivalent of refraction was calculated. True IOP was measured using Goldmann applanation tonometry, tolerant intraocular pressure was calculated by following formula:
$P_0tl = 12.2 + 0.07xDBP – 0.024xAge$ [12], where P_0tl is tolerant intraocular pressure, DBP – diastolic blood pressure, Age – age of patients in years.

Target intraocular pressure was calculated with the help of the next formula:
$P_0targe = 9.5 + 0.07xDBP – 0.024xAge$ [12], where P_0targe is target intraocular pressure, DBP – diastolic blood pressure, Age – age of patients in years.

Visual field examinations were performed with the Humphrey Field Analyzer (program 24-2). MD was used for analysis. Visual field progression of each patient with POAG was analyzed using the method of MD progression per year [13, 14]. A regression analysis of all available MD values during follow-up was performed. The

MD progression per year was calculated. The precondition to analyze the visual field tests was to fulfill the criteria of reliability, that is, false positive fault ≤ 20% and false negative fault ≤ 30%.

In direct binocular ophthalmoscopy was performed with a slit lamp and aspheric ophthalmoscopic lens AOL90D.IOPcontrol was performed after 12, 24hours, on the thirdday,1, 2, 3 and 4 weeks later after the examination and latanoprost prescribtion. 33 participants were selected as the result of further study. These thirty three subjects (forty eyes) aged 43 to 68 years old (average, 54.9±7.17; seventeen men, sixteen women) gave informed consent to take part in the study. In twenty six patients only one eye was examined and in seven patients – two eyes. Inclusion– exclusion criteria were a primary open angle glaucoma (without any other ophthalmic abnormality such as diabetic retinopathy, corneal problems or macular problems), best corrected visual acuity 0,6 and more, IOP was higher than individual tolerance at the background of latanoprost 0,005% usage for 4weeks. The research was performed with the principles of the Helsinki Declaration and was approved by the ethical committees.

Subjects were divided into 2 groups of comparable age, sex, refraction. Groups characteristics are presented in Table 1. In each group the thickness of the ciliary body by ultrasound biomicroscopy was investigated, level of near visual load defined and tolerated correction for near were defined. Maximal thickness of the ciliary body was determined using Sonomed VuMax UBM, in the room lighting, all the patients were instructed to consider the finger.

Amount of near visual load (reading, computer work, etc.) hours during the day in the patients was determined by questioning. In accordance with the results of the questionnaire, patients were devided into four subgroups: 1. insignificant near visual load - near visual load irregular, less than 1 hour per day, 2. low near visual load - up to 3 hours a day 3. moderately high near visual load - from 3 to 6 hours per day, 4. high near visual load - more than 6 hours a day.

Measurement of reading acuity was performed with the help of MNREAD acuity charts. The chart was evenly illuminated and the luminance of the white

background of the charts was80 cd/m2.The MNREAD sentences were shown to patients at the testing distance of 40 cm (16 inches).

An estimate of reading acuity was given by the smallest print size at which the patient can read the entire sentence without making significant errors. After the patient had read as much of the chart as possible, the number of sentences that the patient read or attempted to read was counted. Then the number of words that the patient read incorrectly was counted. For calculating of reading acuity (in logMAR) was using the following formula: Acuity = 1.4 – (sentences×0.1) + (errors×0.01). Reading acuities in logMAR was expressed as a Snellen fraction with the help of application tables.

Results. As a result, the true intraocular pressure was in average19.8 ± 0.83mmHg, which is 16.5% more than the average tolerated pressure and 38.5% more than the target IOP.

It was found, that in the first group three patients (3 eyes) had low near visual load, six patients (7 eyes) – moderately high near visual load, seven patients (10 eyes) – high near visual load. In the second group two patients (3 eyes) had low near visual load, four patients (5 eyes) – moderately high near visual load, eleven patients (12 eyes) – high near visual load. Thus in both groups 85% of the eyes with POAG had moderately high and high near visual load. Uncorrected visual acuity was 0.16±0.08 in the first group, and 0.15±0.07 in the second one. Best corrected visual acuity was 0.68±0.07 in the first group and 0.67±0.06 in the second one. Maximal tolerated near correction was 4.13±2.25 D in group 1 and 4.45±1.88 D in group 2.Maximal ciliary body thickness in both groups was significantly higher than the results received by other authors. Thus Lossing L. A. et al. [15] measured maximal ciliary body thickness by anterior segment OCT and received the results: considering the remote object - 0.795 ± 0.065 mm, considering close objects (0.25 m) - 0.869 ± 0.083 mm. The study was conducted in young people aged 25-28 years. In another study [16]in patients with glaucoma, we measured the maximal thickness of the ciliary body using ultrasound biomicroscopy in similar to our conditions. Subjects were aged 56.8±3.9 years old, and the rate was 0.707±0.03 mm. Earlier we also

studied the maximal thickness of the ciliary body of 128 eyes of patients with primary open-angle glaucoma at the age of 53.14±3.78 years old [17]. Data obtained using ultrasound biomicroscopy for the maximal thickness of the ciliary body were 0.687 ± 0.072 mm.

Thus our results in the first (0.881±0.039 mm) and the second (0.889±0.049 mm) groups were significantly higher than the average in patients with POAG and with the corresponding age in other studies. These results, however, were comparable with measurements of the ciliary body thickness in young healthy people with tense of accommodation. It was also a direct dependence of the ciliary body thickness and the true value of intraocular pressure with a correlation rate r=0.52.

According to the hypothesis of increased intraocular pressure due to accommodative system tone, which is consistent with our data, to reduce intraocular pressure the tone of accommodation should be reduced. For this purpose, we prescribed hypercorrection of presbyopia for the first group of patients with POAG. The correction was made gradually, in steps of 0.25diopters with intervals of 1-2 weeks. If in a week or earlier after increasing near vision correction patients complained of headache, blurring, image distortion, etc., the value of the correction was reduced to 0.25 diopters. As a result, the value of additional correctionaveraged0.5 ± 0.13diopters (from 0.25 to 1.0dioptерswith a median of 0.5 diopters). The magnitude of additional correction was inversely related to age, with correlation r = 0.79. In the second group optical correction as administered with considering of refraction, age and individual tolerability only.

Patients in both groups were followed up with periodic examinations: tonometry was performed monthly and once in three months a visual acuity was checked, perimetry and ophthalmoscopy were made. These examinations were conducted to avoid missing a significant progression of POAG in the observed groups. Significant progression of glaucoma was considered in which the MD according to perimetrywas-0,5 dB for 3 months, i. e.-2 dB per year. If there was a significant decrease in visual function or increase of intraocular pressure, patients were offered various ways of combined antihypertensive therapy, laser or surgical procedures. To

assess the effectiveness of presbyopia overcorrection in reducing IOP one year later tonometry, the checking of visualacuity, perimetry, ophthalmoscopy, the thickness of the ciliary body were estimated. As a result, five patients were excluded from the study: four of them were in the group without hypercorrection and one in the group with overcorrection of presbyopia. Data before and after one year are presented in the table 2.

In the group with hypercorrection the reduction of intraocular pressure (17.3 ± 0.84 mm Hg) was statistically significant ($p < 0.01$), its value was close to the average tolerant IOP (17.0 ± 0.67 mm Hg), but was higher than the target (14.3 ± 0.67 mm Hg). In seven eyes the target pressure was achieved, in five eyes IOP was at the level of tolerance, and in eight eyes it was higher than tolerance. And all eyes reached the target pressure belonged to patients with a high near visual load. In normal correction of presbyopia group no significant IOP changes were observed.

1 year later in the group with hypercorrection a statistically significant ($p < 0.01$) decrease in the thickness of the ciliary body also was observed, more marked in patients with high near visual load ($r = 0.47$). Progression of glaucoma according to perimetry was significantly less ($p < 0.01$) in the group with a hypercorrection of presbyopia as compared with group with ordinary correction. Negative progress of perimetry data was observed in 8 patients whose IOP had higher tolerance.

Conclusions. Overcorrection of presbyopia, as a way to regulate IOP may be in addition to antihypertensive therapy for glaucoma. The advantages of this method is its gentle physiological effects on the system of development and outflow of aqueous humor. However, using this method, lowering IOP is limited by several factors. First, a requirement for compliance to treatment, because of the use of overcorrection in the early stages may be accompanied by some discomfort. To avoid rejection of correction of such patients there should be carried out discussions with the explanation of all the advantages of this method of regulation of intraocular pressure. Second, based on our research, it was found that the greatest impact of presbyopia overcorrection had on ophthalmotonus of glaucoma patients with high visual load (more than 6 hours / day). Patients with moderately high visual load are less affected

by overstated optical correction of persbyopia. This may be associated with more prolonged exposure to the overcorrection of the ciliary muscle tone in patients with high near visual load. However, the role of increased visual load in rigidity of IOP to the effects of prostaglandins seems high because 85% of such subjects had near visual load more than 3 hours a day.

Conflict of Interests. The authors declare that there is no conflict of interests regarding the publication of this paper.

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Резюме. Метою нашого дослідження було вивчення впливу різних рівнів зорового навантаження на рівень внутришньоочного тиску (ВОТ) у хворих на первинну відкритокутову глаукому (ПВКГ), які використовували аналоги простагландинів та оптимізувати їх вплив на відтік водянистої вологи ока.
Матеріал та методи. У дослідження було включено 33 хворих (40 очей) з вперше діагностованою первинною відкритокутовою глаукомою та стійким до латанопросту 0,005 % ВОТ. Ці хворі були попередньо досліджені з визначенням гостроти зору вдалеч та зблизька, рефракції, істинного, толерантного та цільового ВОТ, з виконанням периметрії та офтальмоскопії. Хворих було розподілено на 2 групи, подібні за віком, статтю, рефракцією. В кожній групі було визначено товщину циліарного тіла за допомогою ультразвукової біомікроскопії, а також рівень зорового навантаження зблизька та величину стерпної корекції для близька.
Результати. Було встановлено, що в обох групах 85% очей хворих з ПВКГ мали помірно високе (3-6 годин на день) та високе (більш ніж 6 годин на день) зорове навантаження зблизька. Максимальна товщина циліарного тіла в обох групах була значно вищою, ніж дані, що було отримано іншими авторами: 0.881±0.039 мм у 1 групі і 0.889±0.049 мм у 2-й групі. Також не спостерігалось прямої залежності товщини циліарного тіла та ВОТ (r=0.52). Гіперкорекція далекозорості в першій групі проводилася поступово з кроком 0,25 дптр. Значення додаткової корекції в середньому складало 0,5 ± 0.13 дптр. Величина додаткової корекції була зворотно пов'язана з віком (r=0.79). Для оцінки ефективності гіперкорекції пресбіопії через рік проводилися тонометрія, візометрія, периметрія (MD/год метод), офтальмоскопія, товщина циліарного тіла. В 1 групі спостерігалося зниження ВОТ (17.3 ± 0,84 мм рт. ст.) було статистично значущим (p <0.01), його значення було близьким до середнього показника толерантного ВОТ (17.0 ± 0,67 мм рт.ст.), але було вищим, ніж тиск мети (14.3 ± 0,67 мм рт. ст..). Також в цій групі спостерігалось статистично значуще (p <0,01) зменшення товщини циліарного тіла, що було більш виразне у пацієнтів з високим зоровим навантаженням зблизька (r = 0.47). Прогресування глаукоми за даними периметрії було значно меншим (p <0,01) в групі з гіпркорекцією пресбіопії порівняно з групою зі звичайною корекцією.
Висновки. Гіперкорекція пресбіопії, як спосіб регулювання ВОТ може бути доповненням до антигіпертензивної терапії для пацієнтів з високим зоровим навантаженням з близька та ПВКГ.
Ключові слова: первинна відкритокутова глаукома, резистентний внтришньоочний тиск, рівні зорового навантаження зблизька, корекція пресбіопії, максимальна товщина циліарного тіла.

Резюме. Целью нашего исследования было изучение влияния различных уровней зрительной нагрузки на уровень внутриглазного давления у больных первичной открытоугольной глаукомой, которые использовали аналоги простагландинов и оптимизировать их влияние на отток водянистой влаги глаза.

В результате работы, установлено, что гиперкоррекция пресбиопии, как способ регулирования открытоугольной глаукомы может быть дополнением к антигипертензивной терапии для пациентов с высокими зрительными нагрузками.

Ключевые слова: первичная открытоугольная глаукома, резистентное внутриглазное давление, уровни зрительной нагрузки вблизи, коррекция пресбиопии, максимальная толщина цилиарного тела.

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HYGIENIC FEATURES OF THE INFLUENCE PRODUCED BY A COMPLEX OF ENVIRONMENTAL FACTORS OF NICU ON THE HEALTH OF PREMATURE NEWBORNS

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Abstract: *Hygienic peculiarities of exposure by complex conditions of environmental factors on premature infants in the NICUs have been investigated.*
Key words: *neonatal intensive care units, neonate, prematurity, stress.*

A neonatal intensive-care unit (NICU) is an intensive-care unit specializing in the care of ill or premature newborn infants. The NICU environment provides challenges as well as benefits. Stressors for the infants can include continual and bright light, unfavorable microclimate conditions, and high levels of noise, electromagnetic fields, reduced physical contact, painful procedures, separation from their mothers [1, 2]. A special aspect of NICU stress for both parents and staff is that infants may survive, but with damage of the brain, ears or eyes. Newborn infants may be particularly sensitive to the effects of pain due to the immaturity of neuroanatomical nociceptive system [3, 4, 5].

Objective: to examine the development of premature infants in complex conditions of environmental factors in the NICU.

Research methods: During our research main attention has focused on studying the effects of continual and bright light, unfavorable microclimate conditions, high levels of noise, and electromagnetic fields on the premature infants, who needs nursing in

the NICU for a long period of time. This period can last for several days or several weeks, even months using medical equipment. Our study consisted of 20 premature infants at 25-37 weeks gestation, weighing 2043,35±531,67 grams. Sex distribution of premature infants was 1:1. Participants have been divided into 2 groups: the 1st group (n =10) premature infants in the NICU No. 1 with very high level of a set of physical environmental factors (noise, light, electromagnetic fields, humidity and temperature) and the 2nd group (control) (n =10) premature infants in the NICU No. 2 with low level of physical environmental factors in Kharkov.

Assessment of the light, noise, electromagnetic fields and microclimate conditions: have been conducted by hygienic methods. Sound levels have been measured over the entire spectrum of audible frequencies. The spectrum has been divided into smaller frequency spans, such as octaves or specific narrow bandwidths. Background noise refers to the continuous ambient sound in a space due to the mechanical and electrical systems of the facility or building itself and to permanent equipment. Background noise is produced by sources outside the building and by the building's own heating, ventilation, and air-conditioning systems, vacuum tube systems, elevators, plumbing, automatic doors, etc [6]. Light levels have been measured at each bedside.

APGAR score. A practical method of evaluating the physical condition of a newborn infant shortly after delivery, usually at the 1st and the 5th minutes. APGAR score shows us a number determined by rating the heart rate, respiratory effort, muscle tone, skin color, and response to a catheter, which had gently touched the nostril. Each of these objective signs can receive 0, 1, or 2 points for the maximum best score - 10. The usual Apgar score is 8/9 or 9/9 for a healthy baby. This means the baby had a score of 8 or 9 at the first minute of his life, and at the fifth minutes after his birth, the baby had a score 9. Points are usually taken for the baby’s color [7].

Results and discussion: Scientists study problems of nursing premature infants. However, the medical equipment generating noise and electromagnetic fields, which is in use, disturbs biological rhythms and disrupts microclimate.

The medical equipment generates noise, particularly systems of resuscitation – from 56 to 75 dB, incubators – from 34 to 54 dB, Infusion pumps – from 56 to 63 dB, aspirators – from 53 to 73 dB, artificial lung ventilation – from 53 to 74 dB (Table 1, Figure 1). The highest noise level in the NICU No. 1 – 74 dB, in the NICU No. 2 – 56 dB. Background noise level in the NICU No. 1 – 68 dB, in the NICU No. 2 – 56 dB. It is important, that within any closed space, the sound levels depends by reflections of sound waves from surfaces. When the surfaces are predominantly hard, sound pressure builds up in the space, increasing the original level with reverberation. Conversely, when the surfaces are soft or acoustically absorptive, reflected energy is reduced and sound pressure does not build up.

The compressor has set the highest noise level. In all cases the noise was broadband. Also, when the alarm of monitors was switched the noise was intermittent.

Table 1

Maximum noise levels of medical equipment, dB

Medical equipment	NICU No.1	NICU No. 2
Resuscitation systems	74	56
Incubators	54	34
Infusion pumps	63	56
Aspirators	73	53
Artificial lung ventilation systems	74	53

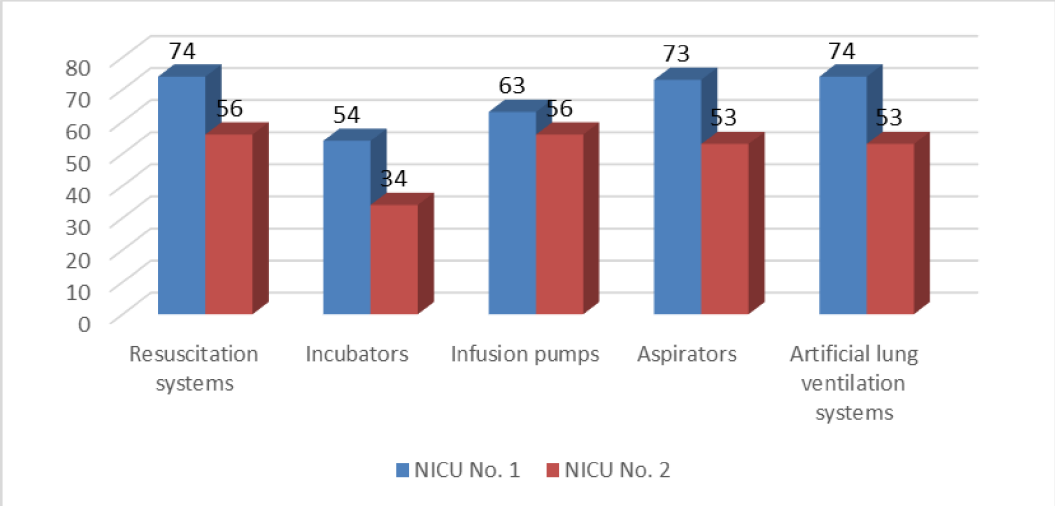

Figure 1. Maximum noise levels of medical equipment, dB

The sources of light generated light levels from 7 to 900 lx in the NICU No. 1, and in the NICU No. 2 – from 200 to 480 lx. There are fluorescent, incandescent and halogen lamps in the NICUs No. 1 and 2. Our studies have confirmed that using double-wall incubators and capes on them decreased light levels from 7 to 15 lx (Table 2).

It is well known that fluorescent, incandescent and halogen lights cause various negative health effects.

The temperature of lamps is the most important characteristic of visible light. There are higher color temperatures, mid-range color temperatures, and lower color temperatures.

Higher color temperatures (4600 K or more) are called daylight colors, which appear blue-white and are associated with vibrancy and feeling of alert.

Mid-range color temperatures (3100 K – 4600 K) look as cool white and are considered friendly and inviting.

Lower color temperatures (up to 3000 K) are called warm white colors, range from red to yellowish-white in tone, and evoke calming, warm and intimate feelings.

For example, the spectrum emitted by incandescent bulbs does not match the sensitivity characteristics of the human eye; the light emitted does not appear white, and most of them are not in the range of wavelengths at which the eye can be the most sensitive. Incandescent lamps are increase brightness and blinding effects.

Table 2

Effectiveness of the proposed methods for reducing brightness of light, lx

Measuring place	Toned light apertures	Levels of artificial light, lx	
		Resuscitation system	Double-wall incubator and capes
NICU No. 1	+	790	30
NICU No. 2	-	25	15

Nocturnal exposure to light in the short wavelength ranges (below 530 nm) generated by fluorescent lamps may interfere with mammalian circadian rhythms due

to its suppressing effect on melatonin production. Fluorescent lamps with magnetic ballasts flicker at a normally unnoticeable frequency of 100 to 120 Hz and this flickering can cause problems for some individuals with a light sensitivity.

Table 3

Physical condition of premature infants, (%)

Group of premature infants	APGAR score					
	1 min.			5 min.		
	10–8	7–5	4–1	10–8	7–5	4–1
NICUNo. 1	-	70	30	10	80	10
NICUNo. 2	-	20	80	20	40	40

But LEDs (light-emitting diode) create a soft, even, and comfortable light. They do not flicker, so do not tire the eyes. Do not emit ultraviolet radiation; their color is similar to daylight. It is very important to the immature structure of preterm infants.

Table 4

Anthropometric measurements of children according to gestation age, (n=10) in the NICU No. 1

Weeks of gestation	Height	Weight	Head circumference	Chest circumference	Body Mass Index	Weight of girls	Weight of boys	Body Mass Index of girls	Body Mass Index of boys
30 – 33	43	1676	30,2	28,5	38,5	1676	-	38,2	-
34 – 36	45,4	2310	30,8	30,1	50,4	2133	2575	47,6	54,5

At the 1st minute 70 % of premature infants had Apgar score of 5-7, and 30 % –"4" in the NICU No. 1 (Table 3). At the 1st minute 20 % of premature infants had Apgar score of 5-7, and 80 % of premature infants – less than "4" as in the NICU No. 2.

At 5th minute of the infants' life 80 % premature infants received Apgar score from "5" to "7", 10 % – less than "4", and 10 % – over "8" in the NICU No. 1. 40 % of

premature infants – from "5" to "7", 40 % – less than "4", and 20 % of premature infants – over "8" in the NICU No. 2.

Anthropometric measurements of premature infants in the NICU No. 1 in the neonatal period and early infancy were more than those in the NICU No. 2, which is explained by higher average age of gestation in the NICU No. 1 in premature infants (33.3 vs. 28.5). The physical parameters of these neonatal period and early infancy, both groups differed from accepted standards weight and growth coefficient and pointed out hypotrophy (Tables 4, 5).

Table 5

Anthropometric measurements of children according to gestation age, (n=10) in the NICU No.2

Weeks of gestation	Height	Weight	Head circumferenc	Chest circumferenc	Body Mass Index	Weight of girls	Weight of boys	Body Mass Index of girls	Body Mass Index of boys
26 – 27	32	952	24,2	21,6	33,6	886,17	1050	26,6	33,5
28 – 31	38,4	1332	26,8	24,8	29,4	1377,5	1150	34,25	31

According to the child development, which depends on environmental factors, we have studied anthropometric measurements in preterm infants during the highest rate of growth and development of the child's body, namely in infancy and early childhood (Tables 6, 7). The average age of the infancy in group 1 - 5.4 months, in-group 2 - 5.4 months. Thus, early childhood in group 1 - 21 months, in group 2 - 20 months. In infancy established weight loss in the 1st group: 6730 and in the 2nd group: 6895.7. Also we can see a decrease level in growth: 64.3 - 1st group against 64.5 in 2nd group of children. This trend was observed among 4625 boys in the 1st group vs. 6406.7 boys in the 2nd group and 7033 girls vs. 7162.5. In early childhood, different weight loss were set too, as we can see 10110 in the first group against 10550 (the 2nd group) and a decrease in a body growth 78.2 vs 84.3.

Table 6

Anthropometric measurements of children in the dynamics (n=10) in the NICU No. 1

The period of Observation:	Height	Weight	Head circumference	Chest circumference	Weight of girls	Weight of boys
Infancy	63,4	6730	41,4	41,8	7033	4625
Early childhood	78,2	10110	46	47	10110	-

Table 7

Anthropometric measurements of children in the dynamics (n=10) in the NICU No. 2

The period of Observation:	Height	Weight	Head circumference	Chest circumference	Weight of girls	Weight of boys
Infancy	64,5	6895,7	41,86	42,7	6812,5	6406,7
Early childhood	84,3	10550	45,6	47	10550	-

The error of anthropometric indicators cannot be considered as signs of health. It is well known that in modern conditions, such as accelerated, same as retarded development of children should be considered as a risk factor for a pathological disease. The data, which showed that the standard deviation of a group of children, who were nursed in the NICU with higher levels of environmental factors may be a manifestation of violation of regulatory mechanisms of energy and metabolic level, which take place at an unsatisfactory adaptation level and what is even worse, failure of adaptation of the body. Children who were nurse in the NICU No. 1 had most of

all disharmonious development, compared with children who were nurse in the NICU No. 2.

Conclusions:

1. It is shown that increased level of environmental factors may have a negative influence on the performance for the harmonious children development, which will risk factor of pathology in the future.
2. The noise should be considered as a factor that can complicate nursing of premature infants. Effects of bright light may cause the violation of growth, development and differentiation of the visual analyzer in premature infants.
3. Incubators and capes are reducing lighting levels to 760 lx and should be encouraged to reduce the effects of bright light in the neonatal intensive care units.

Recommendations:

Ambient lighting levels in infant spaces should be adjustable through a range of at least 10 but not more than 600 lx, as measured at each bedside. Both natural and electric light sources should have controls that allow immediately darkening of any bed position sufficient for trans illumination, when it is necessary. The sources should avoid unnecessary ultraviolet or infrared radiation by the use of appropriate lamps, lens, or filters. Any lighting used outside the infant care area should be located so as to avoid any infant's direct line of sight to the fixture.

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Резюме. Досліджені гігієнічні особливості впливу комплексу чинників навколишнього середовища на здоров'я недоношених дітей у відділеннях реанімації та інтенсивної терапії новонароджених.
Ключові слова: відділення реанімації та інтенсивної терапії недоношених новонароджених, недоношений новонароджений, недоношеність, стрес.

Резюме. Исследованы гигиенические особенности влияния комплекса факторов окружающей среды на здоровье недоношенных детей в отделениях реанимации и интенсивной терапии новорожденных.
Ключевые слова: отделение реанимации и интенсивной терапии недоношенных новорожденных, недоношенный новорожденный, недоношенность, стресс.

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