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E-mail: nila@vnmue.edu.ua

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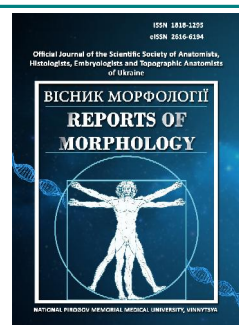
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Microscopic and histochemical changes in the liver of adult rats with hyperhomocysteinemia

Maievskiy O. Ye.¹, Halahan Yu. V.²

¹"Institute of Biology and Medicine" of Taras Shevchenko National University, Kyiv, Ukraine

²National Pirogov Memorial Medical University, Vinnytsya, Ukraine

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CORRESPONDING AUTHOR

e-mail: maevskyalex8@gmail.com

Maievskiy O. Ye.

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Violation of amino acids metabolism in the human body is the cause of changes in the structure and functions of almost all vital organs and systems. During the last tens of years, significant efforts of scientists have been directed to the in-depth study of such compound as homocysteine (Hcys), which is a thiol-containing amino acid and is produced endogenously during the exchange of methionine and cysteine. Under the conditions of its normal concentration (5-15 $\mu\text{mol/l}$), it does not pose a threat to the life and health of living organisms. However, in a number of pathological conditions, a pronounced increase of Hcys in blood plasma and inside cells is registered, which leads to the appearance or progression of diseases, including damage of liver tissue. The aim of the research is to study the microscopic and histochemical changes in the liver of adult rats with hyperhomocysteinemia (HHcys). The experiment was conducted on 22 white non-linear adult male rats aged 6-8 months. During the study, the animals were divided into two groups - control and experimental. Chronic resistance to HHcys was modeled by administering thiolactone Hcys in a dose of 200 mg/kg of body weight intragastrically for 60 days to the rats of the experimental group. Histological preparations were studied using a SEO SCAN light microscope and photo-documented using a Vision CCD Camera with a system of image output from histological preparations. Succinate dehydrogenase was detected histochemically according to the Nakhlash method. These studies were carried out on sections made in a cryostat microtome from unfixed tissue using nitro blue tetrazole. To study the specifics of glycogen accumulation in hepatocytes, sections were stained using Schiff's reagent, after preliminary treatment with iodic acid (PAS reaction) in the Shabadash modification. It was established that the administration of thiolactone Hcys to young rats at a dose of 200 mg/kg led to an increase in the volume of connective tissue elements around the lobules and in the portal tracts of the liver. Thus, it was established that in the liver of adult rats with HHcys, there is a noticeable thickening of the fibrous connective tissue around the lobules and in the portal tracts, trabeculae dissociation, and the appearance of foci of necrosis of the parenchyma of the organ. Hypertrophy and hyperplasia of smooth myocytes in the middle layer and fibrosis of the outer layer of the wall of interlobular arteries, leukocyte infiltration in the portal tracts are observed. A significant decrease in succinate dehydrogenase activity was established histochemically.

Keywords: hyperhomocysteinemia, liver, liver plates, fatty dystrophy, succinate dehydrogenase, rats.

Introduction

Violation of amino acids metabolism in the human body, as established, is the cause of changes in the structure and functions of almost all vital organs and systems. For tens of years, significant efforts of scientists have been directed to the in-depth study of such a compound as Hcys, which is a thiol-containing amino acid and is produced endogenously during the exchange of methionine and

cysteine. Hcys in blood plasma is able to be in protein-bound (99 %) and free (1 %) forms. Under the conditions of its normal concentration (5-15 $\mu\text{mol/l}$), it does not pose a threat to the life and health of living organisms. However, in a number of pathological conditions, a pronounced increase of Hcys is registered in blood plasma and inside cells. This condition is called HHcys and is often used as

a prognostic factor for the risk of cardiovascular diseases, diseases of the respiratory, excretory, and digestive systems, as well as screening for congenital defects of methionine metabolism, miscarriage, vitamin deficiency [4, 8, 9, 18].

The liver and kidneys are the key organs where processes of Hcys metabolism take place. In the presence of any structural and functional changes in the specified organs, deficiency of enzymes of Hcys metabolism (congenital or acquired) or insufficiency of vitamins that play the role of cofactors in these biochemical transformations (B_6 , B_9 , B_{12}), the concentration of Hcys begins to increase [20, 21]. The negative effects of HHcys are now largely established. They consist in homocysteinilation of blood plasma proteins, disruption of methylation processes, stimulation of NMDA receptors, Toll-like receptors (mainly TLR_4), dysregulation of Ca^{2+} -channels, and increased activity of NADPH oxidase. The latter fact is associated with excessive production of reactive oxygen species (ROS). ROS, in turn, trigger signaling pathways and the production of pro-inflammatory mediators - IL-1, IL-6, TNF- α , etc. In addition, HHcys leads to impaired synthesis and reduced bioavailability of NO in endothelial cells of vessel walls [18, 22]. The result of the effect of Hcys on the body is the development of myocardial infarction, disorders of cerebral blood circulation, neurodegenerative diseases [6, 10, 12, 13].

Research conducted on animals, as well as clinical observations, indicate the fact that HHcys serves as the basis for the development of not only the above-mentioned diseases, but in one way or another is a trigger of pathological processes in other body systems. In particular, there is increasing evidence that Hcys disrupts intracellular lipid metabolism, leading to their accumulation in hepatocytes [18]. This leads to the appearance of fatty hepatitis and changes in the morpho-functional parameters of the organ. A change in the structure of the liver leads to disturbances in the mechanisms of utilization of Hcys, and, therefore, becomes the cause of an even greater increase of it in the blood plasma and the progression of existing diseases. Separate literature sources also demonstrate the participation of the specified amino acid in the occurrence of cirrhosis and liver fibrosis. Thus, an urgent task is to study the peculiarities of histological changes in the organ against the background of a long-term increase in the level of Hcys in the blood plasma [2, 16, 17, 19].

The aim of the research is to study of microscopic and histochemical changes in the liver of adult rats with HHcys.

Materials and methods

The study was carried out in compliance with international recommendations on conducting medical and biological research using animals (Kyiv, Ukraine, 2001) and agreed with the provisions of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, France, 1986) [3]. The experiment was conducted on 22

white non-linear adult male rats aged 6-8 months. During the study, the animals were divided into two groups - control and experimental. Chronic resistance HHcys was modeled by administering thiolactone Hcys in a dose of 200 mg/kg of body weight intragastrically for 60 days to the rats of the experimental group. Animals were anesthetized by decapitation using thiopental anesthesia. For histological examination, pieces of liver were taken from pre-weighed animals of all groups. The pieces were fixed in a 10 % formalin solution, not exceeding the exposure duration of 1-2 days. Next, the pieces were dehydrated in alcohols of increasing concentration and embedded in paraffin blocks. The prepared sections, 4-5 μ m thick, were stained with hematoxylin and eosin and methylene blue [1]. Histological preparations were studied using a SEO SCAN light microscope and photo-documented using a Vision CCD Camera with a system of image output from histological preparations.

To study the dynamics of compensatory and adaptive processes of the liver under conditions of HHcys, the study of the key enzyme of the tricarboxylic acid cycle - succinate dehydrogenase - is of particular interest. This mitochondrial enzyme was detected histochemically by the method of Nakhlas [5]. These studies were carried out on sections made in a cryostat microtome from unfixed tissue using nitro blue tetrazole. The sediment in the form of blue granules of diformazan testified to the presence and localization of the enzyme.

To study the specifics of glycogen accumulation in hepatocytes, sections were stained using Schiff's reagent, after pre-treatment with iodic acid (PAS reaction) in Shabadash's modification [5].

Results

Studies of the microscopic organization of the liver of mature animals with hyperhomocysteinemia revealed more pronounced structural changes in the organ compared to young animals. A noticeable thickening of the fibrous connective tissue around the lobules and in the portal tracts was established. Dyscompletion of liver plates was revealed. In hepatocytes, the nuclei were hyperchromic, pyknotically altered. Signs of hydropic and fatty dystrophy were observed in the cytoplasm of hepatocytes. In some places, foci of necrosis of the liver parenchyma were found. Significant changes are also present in the vascular bed of the liver of mature animals. In the vast majority of central, sublobular and interlobular veins, full blood was found, their walls were expanded and thinned (Fig.1).

The thickness of the wall of interlobular arteries increased due to hypertrophy and hyperplasia of smooth myocytes in the tunica media and fibrosis of the tunica adventitia. There is leukocyte infiltration in the portal tracts. Significant changes were found in the microcirculatory bed of the liver. The lumens of the sinusoids were expanded, often filled with formal elements. Endothelial cells were

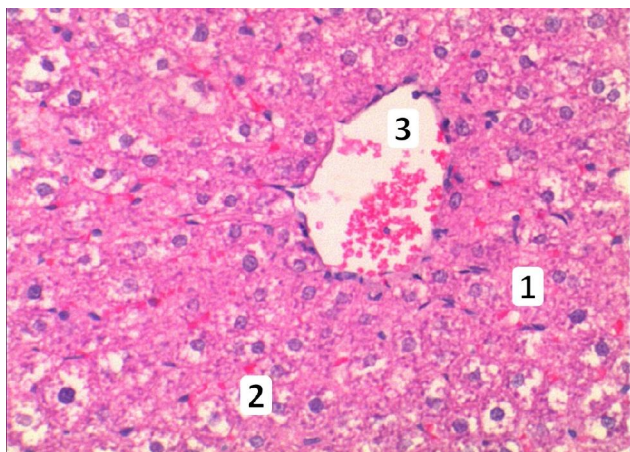


Fig. 1. Histological changes in the liver of mature animal after simulated hyperhomocysteinemia. 1 - violation of the hepatocyte plates organization of the organ, 2 - dystrophically changed hepatocytes, 3 - enlarged central vein. Staining with hematoxylin and eosin. x200.

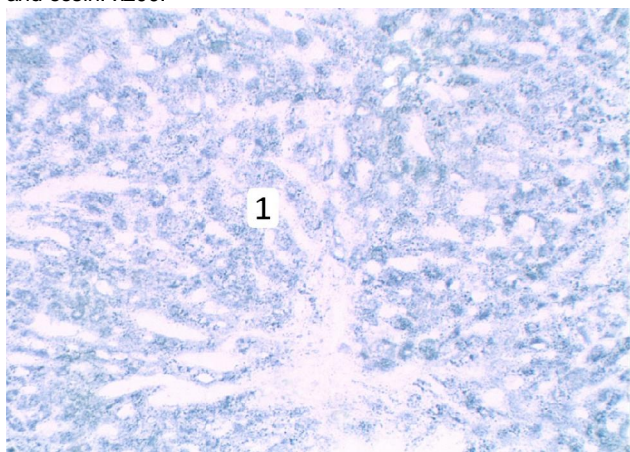


Fig. 2. Low activity of succinate dehydrogenase in the liver of a mature animal under conditions of simulated hyperhomocysteinemia. 1 - in the cytoplasm of most hepatocytes, there were few clumps of diformazan. Nakhlash method. x 200.

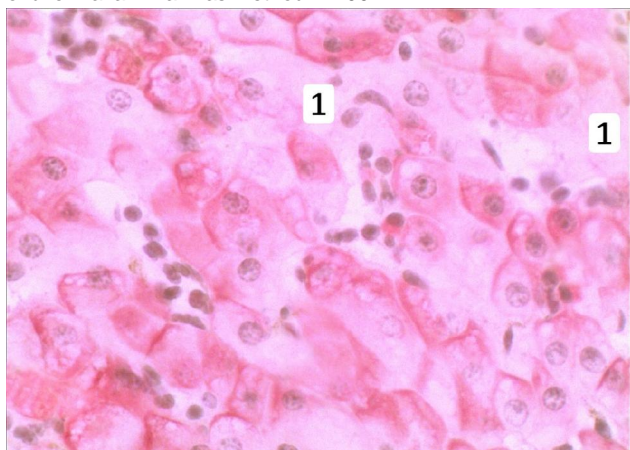


Fig. 3. The presence of glycogen in the liver of a mature animal under conditions of simulated hyperhomocysteinemia. 1 - low content of glycogen lumps in the cytoplasm of hepatocytes. Shabadash method. x400.

partially damaged, their nuclei were hyperchromic, pyknotically altered, and the cytoplasm was swollen and uneven. Perisinusoidal spaces are expanded, infiltrated by leukocytes and macrophages.

A significant decrease in succinate dehydrogenase activity was established histochemically. There were few lumps of diformazan in hepatocytes, they were weakly basophilic (Fig. 2).

Histochemical study of the presence of glycogen in the hepatocytes of the liver of mature animals under the conditions of simulated hyperhomocysteinemia showed a decrease in the content of the indicated trophic compound in the cytoplasm of cells, in some cells the cytoplasm is practically devoid of this trophic compound (Fig. 3).

Discussion

Related studies conducted on experimental animals accompanied by simulation of chronic HHcys showed a negative effect of this amino acid on the structural and functional indicators of various body systems.

It was established that in adult rats with persistent HHcys, the organs of the respiratory system underwent changes in the form of the development of dyscirculatory disorders, remodeling of bronchiole walls, and inflammatory processes. The lumens of the bronchi were narrowed, spasmodic, filled with serous-mucous contents. Desquamation of the epithelial lining in their lumen was found in some places. The bronchial walls were swollen, infiltrated with histiocytic cells, neutrophils, and lymphocytes. Zones of dysatelectases and atelectasis in the respiratory department were a characteristic finding. Zones of emphysematous-changed areas of lung tissue were also detected. Under these conditions, HHcys was associated with an increase in the activity of fibroblasts and thickening of the walls of the alveoli, which led to a violation of normal gas exchange. This process was complicated by damage of the vessel walls, and, therefore, to the components of the air-blood barrier [15].

R. F. Kaminsky et al. [7] studying the structure of the heart of laboratory animals under conditions of HHcys at the submicroscopic level revealed damage of the organ in the form of its dystrophic and destructive changes. Endocardium and myocardium were involved in the pathological process. The first was characterized by thickening of collagen fibers and significant swelling of the components of the main substance. In the myocardium, cardiomyocytes underwent pronounced changes. They lost myofibrils, sarcomeres were disorganized. Mitochondria of the cells were swollen, their matrix was illuminated, and the crystals showed signs of destruction. The tubules of smooth ER expanded significantly. The components of the connective tissue also actively increased their volume in the myocardium, in particular, the thickening of collagen fibers was recorded. Violation of the structural organization of vessels of the microcirculatory bed of the myocardium was observed.

Recent studies [14] have shown the presence of a relationship between biochemical changes in thyroid tissue and the level of Hcys in the blood plasma of experimental rats. HHcys in animals was accompanied by the development of catabolic processes, which were characterized by the accumulation of low-molecular-weight compounds in the blood and homogenates of the thyroid gland. Biochemical studies also revealed the activation of proteolytic processes in the organ, which was evidenced by an increase in the levels of matrix metalloproteinases (MMP-2). Also, proteolysis in the tissue of the thyroid gland was confirmed by a significant shift in the protein profile. The accumulation of proteins with a molecular weight <30 kDa and a decrease in high molecular weight proteins were recorded. The activation of inflammatory processes was characteristic and confirmed by the increase of the corresponding cytokines [14].

Ultramicroscopic studies of liver tissue under conditions of HHcys against the background of hypo- and hyperthyroidism demonstrated the presence of significant disturbances in microcirculation and transcapillary exchange in the organ. At the same time, hepatocytes were characterized by damage of the nuclei and cytoplasm

structure. Similar rearrangements were observed in the endotheliocytes of the blood vessels vascular walls of the liver. The authors note that compensatory and adaptive, destructive and necrotic changes developed in the organ. The components of the nuclei and organelles of hepatocytes underwent irreversible changes, which ultimately led to a violation of the synthetic and detoxification functions of the liver [10, 11].

Conclusion

1. In adult rats, the simulation of the HHcys state led to an increase in the volume of connective tissue elements around the lobules and in the portal tracts of the liver. Disassembly of the liver plates, changes in the nuclear apparatus of hepatocytes, the development of their hydropic and fatty dystrophy, areas of necrosis of the tissue of the organ, changes in the structure of vessels, and disruption of microcirculation processes were characteristic.

2. Histochemical studies under these conditions established a decrease in the activity of succinate dehydrogenase of mitochondria and the content of glycogen in the cytoplasm of hepatocytes.

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МІКРОСКОПІЧНІ ТА ГІСТОХІМІЧНІ ЗМІНИ ПЕЧІНКИ ДОРΟΣЛИХ ЩУРІВ З ГІПЕРГОМОЦИСТЕЇНЕМІЄЮ

Маєвський О. Є., Галаган Ю. В.

Порушення метаболізму амінокислот в організмі людини є причиною зміни структури та функцій майже всіх вітальних органів і систем. Впродовж останніх десятиріч років значні зусилля науковців спрямовані на поглиблене вивчення такої сполуки як гомоцистеїн (Гц), що є тіоплімісною амінокислотою та продукується ендогенно в ході обміну метіоніну й цистеїну. За умов його нормальної концентрації (5-15 мкмоль/л) він не становить загрози для життя та здоров'я живих організмів. Однак, за умови виникнення низки патологічних станів реєструють вірогідне збільшення концентрації Гц у плазмі крові та всередині клітин, що призводить до появи чи прогресування хвороб, в тому числі ураження тканини печінки. Метою дослідження стало встановлення мікроскопічних та гістохімічних змін печінки дорослих щурів з гіпергомоцистеїнемією (ГГц). Експеримент проведений на 22 білих нелінійних дорослих щурах-самцях, віком 6-8 місяців. При дослідженні тварин розподіляли на дві групи - контрольну і дослідну. Хронічну стійку ГГц моделювали введенням щурам дослідної групи тіоплактону Гц в дозі 200 мг/кг маси тіла інтрагастрально впродовж 60 діб. Гістологічні препарати вивчали за допомогою світлового мікроскопа SEO SCAN та фотодокументували за допомогою відеокамери Vision CCD Camera з системою виводу зображення з гістологічних препаратів. Гістохімічно виявляли сукцинатдегідрогеназу за методом Нахласа. Ці дослідження здійснювали на зрізах, виготовлених в мікромом-кріостаті з нефіксованої тканини з використанням нітро-синього тетразолу. Для дослідження особливостей накопичення глікогену в гепатоцитах проводили забарвлення зрізів за допомогою реактиву Шиффа, після попередньої обробки йодною кислотою (PAS-реакція) в модифікації Шабадаша. Введення тіоплактону Гц молодим щурам в дозі 200 мг/кг призводило до збільшення об'єму елементів сполучної тканини навколо часточок та в портальних трактах печінки. Таким чином, встановлено, що у печінці дорослих щурів з гіпергомоцистеїнемією відбувається помітне потовщення волокнистої сполучної тканини навколо часточок та у складі портальних трактів, дисконплектація печінкових балок, поява осередків некрозу паренхіми органу. Спостерігаються гіпертрофія та гіперплазія гладких міоцитів у середній оболонці та фіброз зовнішньої оболонки стінки міжчасточкових артерій, лейкоцитарна інфільтрація в портальних трактах. Гістохімічно встановлене значне зниження активності сукцинатдегідрогенази.

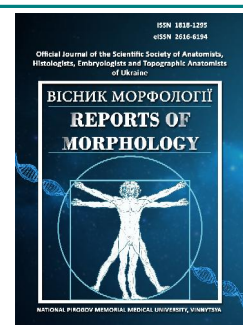
Ключові слова: гіпергомоцистеїнемія, печінка, печінкові пластинки, жирова дистрофія, сукцинатдегідрогеназа, щури.



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Modeling of Valsalva sinuses and coronary artery ostia height parameters, depending on age-anthropometric indicators in healthy men based on computed tomography

Pidvalna U. Ye.

Danylo Halytsky Lviv National Medical University, Lviv, Ukraine

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CORRESPONDING AUTHOR

e-mail: pidvalna_uliana@meduniv.lviv.ua
Pidvalna U. Ye.

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Computed tomography is the "gold standard" for performing aortic morphometry during preoperative planning in invasive cardiology and cardiac surgery. Predictive modeling of indicators can significantly save resources. The purpose of the study: to make modelling of Valsalva sinuses and coronary artery ostia height parameters depending on age-anthropometric indicators in healthy men based on computed tomography. The material is represented by contrast-enhanced computed tomography images of the aorta and coronary arteries of forty-three men under normal conditions. Methods: morphometric and statistical analyses. A multifactorial correlation-regression analysis was conducted to establish the complex influence of age-anthropometric parameters on sinuses of Valsalva and coronary artery ostia height. The reliability of the obtained indicators was confirmed by Fisher's test (F). Using the Durbin-Watson autocorrelation criterion, the correctness of the built model was proved. In healthy men, weight (direct effect) and body mass index (inverse effect) significantly influenced the height of the lower edge of the right coronary artery ostia. The regression coefficient is $R = +0.632$, with $p < 0.001$, the standard error of estimation (SEE) is 2.951. The obtained linear equation of the prognostic model: the level of the height of the departure of the lower edge of the right coronary artery ostia = $0.359 \times A1 - 1.099 \times A2 + 16.53$. The correctness of the built model was checked using the Durbin-Watson autocorrelation test (2.181). The prognostic model for calculating the height of the left aortic sinus was formed by height and weight indicators (strong direct influence): $R = +0.759$, $p < 0.001$, $SEE = 2.208$. The adjusted coefficient of multiple determination was $R^2_{adj} = +0.562$. The Durbin-Watson autocorrelation criterion was within the normal range (2.241). The linear equation of the prognostic model with the obtained β -coefficients: the level of the height of the left sinus of the aorta = $35.83 \times A1 + 0.033 \times A2 - 42.22$. The work of prognostic models for individuals with different anthropometric and age parameters was verified. Thus, a model of the dependence of the indicator of the height of the left sinus of the aorta on height and weight was created; of the height of the deviation of the lower edge of the right coronary artery from weight and body mass index in healthy men based on computed tomography.

Keywords: coronary artery ostia, anatomy, computed tomography, aorta.

Introduction

According to the Global Burden of Disease (GBD), mortality from cardiovascular diseases in Ukraine is 64.3 % [15, 19]. It is important that the sex aspect is clearly observed in the structure of morbidity. Men get sick more often than women. This tendency is typical in the global and Ukrainian incidence structure. In Ukraine, men have almost twice the incidence rate. According to the European society of cardiology (ESC) 772.1 cases per 100,000 men

and 440.9 per 100,000 women) (2017 data) [1, 2].

Computed tomography (CT) is the "gold standard" modality for diagnosing the state of the cardiovascular system [10, 18]. Morphometry of the aortic bulb is necessary for preoperative planning in invasive cardiology and cardiac surgery [3, 7]. Morphometric data of the aorta differ between countries, while research on this topic in Ukraine is rather isolated. However, an increase in the number of performed

diagnostic procedures will necessitate a quick and, most importantly, detailed analysis of the cardiovascular system, measurements of target structures. Modeling is one option that can significantly save radiologists' time and reduce overall economic costs.

Using CT images, in previous studies, we performed a morphometric analysis of the aortic bulb and established a correlation between the values of the height of the aortic sinuses, the height of the exit of the coronary arteries and anthropometric indicators in healthy men [11, 12]. The results of the research led to the next stage - prognostic modeling of height indicators, to prove the correctness of the constructed logical model and to test it by calculating the predicted values of vascular parameters for two men with different anthropometric and age parameters without damage to the cardiovascular system, who were interpreted as the norm.

The purpose of the study: to make modelling of Valsalva sinuses and coronary artery ostia height parameters depending on age-anthropometric indicators in healthy men based on computed tomography.

Materials and methods

For the purpose of prognostic modeling of Valsalva sinuses height parameters depending on age and anthropometric parameters, a multifactor correlation-regression analysis was performed to establish the complex influence of age-anthropometric parameters on the parameters of the studied structures.

This is a single-center, prospective study conducted on the basis of the Lviv Regional Clinical Hospital and the Ukrainian-Polish Heart Center "Lviv" from 2019 to 2022. Inclusion criteria: male subjects (1) who underwent computed tomography (CT) with coronary contrast arteries and aorta (2), without structural changes in the heart and aorta that could potentially affect the measurements (3). Exclusion criteria: birth defects, structural changes of the studied structures, history of cardiac surgery, artifacts, incomplete clinical data. 43 persons included in the study met the set criteria.

Measurements have been made: sinuses of Valsalva height (distance from the aortic valve annulus to the sinotubular junction) and coronary artery ostia height (distance from the aortic valve annulus to the lower edge of the coronary artery ostia) were performed at a CT station with licensed software (General Electric, USA). Diagnostic modality: tomograph LightSpeed VCT XT, GE (General Electric, USA). Contrast agent - Ultravist 470 (Bayer Healthcare, Germany). Data taken into account: age, height, body weight, body mass index, body surface area (calculated according to the Mosteller formula).

Primary data were based on morphometric analysis of the height of the right sinuses of Valsalva (1), left sinuses of Valsalva (2), posterior sinuses of Valsalva (3), coronary artery ostia height (4), left coronary artery ostia height (5) in men without lesions of the heart and ascending aorta

(normal), which underwent a computed tomography (CT) study with contrast of the aorta, heart, and coronary arteries. Predictors of influence: age (1), height (2), weight (3), body mass index (4), body surface area (5).

The study was conducted in accordance with the Declaration of Helsinki "Ethical principles of medical research with human participation as a research object" and was approved at the meeting by the conclusion of the Bioethics Commission of Danylo Halytsky Lviv National Medical University (protocol No. 10 of December 20, 2021).

Statistical analysis was performed using R software version 4.0.5 (R Core Team, 2021) and R Commander (version 2.7-2, GNU General Public License) based on the Windows operating system. We calculated the regression coefficient (R), the adjusted coefficient of multiple determination R^2_{adj} , which would prove the influence of the specified predictors in X % of cases. The reliability of the obtained indicators was confirmed by Fisher's test (F). Using the Durbin-Watson autocorrelation criterion, the correctness of the built model was proved. The results of logistic regression calculations for predicting the level of vascular parameters were presented in the form of tables and presented graphically. For clarity of operation of the logistic model, it was tested by calculating the predicted values of vascular parameters for two individuals from the research group who differ in anthropometric and age parameters.

Results

The age and anthropometric characteristics of men ($n = 43$) under normal conditions are presented in Table 1. A multifactorial regression analysis was performed for each vascular parameter (dependent predictors) of healthy men with the selection of the most optimal set of independent predictors of influence (age and anthropometric indicators), which reliably strongly influenced value of each morphometric parameter in healthy men. During the study, the most optimal balanced two forecasting models were selected by stepwise selection: for the value of the height of the lower edge of the right coronary artery ostia and for the height of the left sinuses of Valsalva, which were confirmed by the appropriate reliability criteria.

It was established that the height of the lower edge of the right coronary artery ostia was significantly influenced

Table 1. Age and anthropometric characteristics of men without structural damage to the heart and ascending aorta during a computed tomography study.

Parameters	Men ($n = 43$)
Age (years)	52.56±13.52
Height (m)	1.756±0.067
Weight (kg)	84.74±14.14
Body mass index (kg/m ²)	27.54±4.74
Body surface area (m ²)	2.033±0.181

Table 2. Results of logistic regression calculations for predicting the level of the height of the lower edge of the right coronary artery ostia in healthy men.

Indexes	Conventional designation	b-coefficients	p
Constant		16.53	<0.001
Weight	A1	0.359	<0.001
Body mass index	A2	-1.099	<0.001

by weight (direct influence) and body mass index (inverse influence). The regression coefficient is $R = +0.632$, with $p < 0.001$ (according to Fisher), the standard error of estimation (SEE) is 2.951. The adjusted coefficient of multiple determination $R^2_{adj} = +0.361$ indicates that the complex influence of independent predictors of weight and body mass index on the value of the height of the lower edge of the right coronary artery ostia was present in 36.02 % of cases in healthy men. The main data for building the model are given in Table 2.

By substituting the calculation data from the table, we get a linear equation of the prognostic model: *the height level of the coronary artery ostia lower right edge* = $0.359 \times A1 - 1.099 \times A2 + 16.53$.

The correctness of the built model was checked using the Durbin-Watson autocorrelation criterion, the obtained value of 2.181 is within the normal range (1.5-2.5).

The calculated average predicted value of the height of the lower edge of the eye of the right coronary artery is 16.67 ± 2.31 mm (minimum value 11.59 mm, maximum 21.30 mm), which actually completely coincides with the available average value of healthy men: 16.67 ± 3.69 mm.

A graphic representation of the normal probability of the influence of the obtained independent anthropometric predictors on the predicted value of the height of the lower edge of the right coronary artery ostia in healthy men is presented in Figure 1.

To practically confirm the work of this prognostic model,

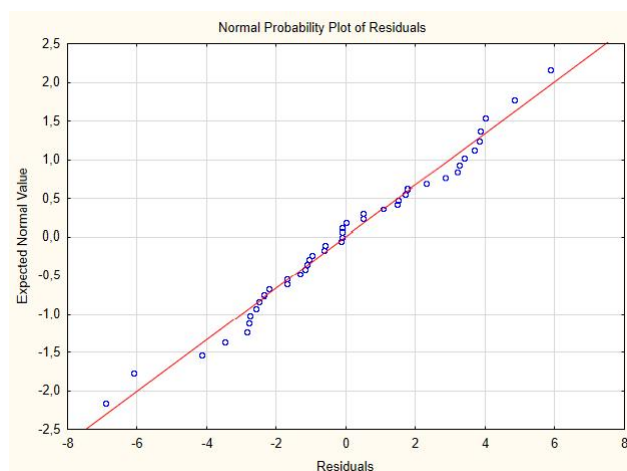


Fig. 1. The normal probability of influence of predictors of weight and body mass index on the predicted value of the height of the lower edge of the right coronary artery ostia in healthy men.

we will consider two real examples of calculations for different anthropometric and age parameters of the studied persons.

Example № 1. Person No. 10 from the database of healthy men: man, 65 years old, height 1.81 m, weight 90 kg, body mass index 27.47 kg/m², body surface area 2.127 m², height of the lower edge of the right coronary artery ostia 18.50 mm.

We substitute the necessary weight and body mass index data into the formula of the linear logistic regression equation and get the result: *height level of the right coronary artery ostia* = $0.359 \times 90.00 - 1.099 \times 27.47 + 16.53 = 18.62$ mm.

Comparing the actual (18.50 mm) and predicted (18.62 mm) value of the height of the lower edge of the right coronary artery ostia, we get a difference of 0.12 mm, which does not exceed the permissible 5 % error.

Example № 2. Person No. 43 from the database of healthy men: man, 44 years old, height 1.65 m, weight 85 kg, body mass index 31.22 kg/m², body surface area 1.974 m², height of the lower edge of the right coronary artery ostia 12.60 mm.

Enter the required personal data into the linear logistic regression equation: *height level of the right coronary artery ostia* = $0.359 \times 85.00 - 1.099 \times 31.22 + 16.53 = 12.71$ mm.

Thus, the calculated value of the height of the lower edge of the right coronary artery ostia of 12.71 mm differs slightly from the actual value of 12.60 mm obtained during the CT scan - the difference is 0.11 mm, which confirms the effectiveness of this prognostic model in practice.

To form a prognostic model for calculating the height of the left sinus of Valsalva in healthy men, a set of independent predictors was optimal, which included height and weight indicators (strong direct influence): $R = +0.759$, $p < 0.001$, $SEE = 2.208$. The adjusted coefficient of multiple determination was $R^2_{adj} = +0.562$, which confirms the dependence of the value of the height of the left sinus of Valsalva in 56.09 % of cases on the age-anthropometric indicators of healthy men. The Durbin-Watson autocorrelation criterion was within the normal range - 2.241. The necessary data for building the model are given in Table 3.

The linear equation of the prognostic model with the obtained β -coefficients will have the following form: *left sinus of Valsalva height level* = $35.83 \times A1 + 0.033 \times A2 - 42.22$.

The calculated average predicted value of the height of the left sinus of Valsalva is similar to the actual value: 23.49 ± 2.54 mm and 23.49 ± 3.33 mm, respectively. The minimum prognostic value is 17.41 mm, the maximum is 28.95 mm.

Figure 2 shows a graph of the normal probability of the influence of the obtained independent anthropometric predictors on the predicted value of the height of the left sinuses of Valsalva in healthy men.

We will test the performance of the prognostic model on two individuals with different anthropometric and age

Table 3. Results of logistic regression calculations for predicting the height of the left sinus of Valsalva in healthy men.

Indexes	Conventional designation	b-coefficients	p
Constant		-42.22	<0.001
Weight	A1	35.83	<0.001
Body mass index	A2	0.033	>0.05

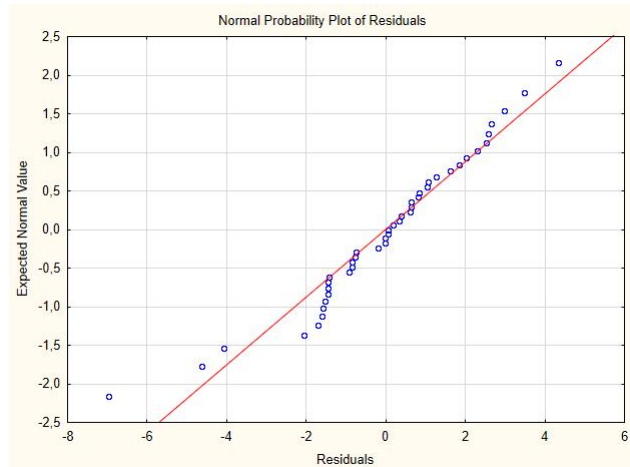


Fig. 2. The normal probability of influence of predictors of height and weight on the predicted value of the height of the left sinus of Valsalva in healthy men.

parameters.

Example № 3. Person No.13 from the database of healthy men: male, 49 years old, height 1.65 m, weight 65 kg, body mass index 23.88 kg/m², body surface area 1.726 m², left aortic sinus height 19.10 mm.

Enter the height and weight of the person into the formula and get the result: *left sinus of Valsalva height level* = 35.83 x 1.65 + 0.033 x 65.00 - 42.22 = 19.04 mm. The obtained predicted value of the height of the left sinus of Valsalva (19.04 mm) does not significantly differ from the actual (19.10 mm) level of the parameter of this vessel (p>0.05).

Example № 4. Person No. 41 from the database of healthy men: male, 53 years old, height 1.84 m, weight 80 kg, body mass index 23.63 kg/m², body surface area 2.022 m², left sinus of Valsalva height 26.40 mm.

We substitute the relevant personal data into the linear regression equation: *left sinus of Valsalva height level* = 35.83 x 1.84 + 0.033 x 80.00 - 42.22 = 26.34 mm.

Therefore, comparing the forecast (26.34 mm) and the actual value (26.40 mm), we get an insignificant difference between the indicators of 0.06 mm, which proves the effectiveness of this forecast model.

Discussion

Modeling of parameters of Valsalva sinuses and coronary artery ostia height depending on age-anthropometric parameters in forty-three healthy men was carried out. It is based on the morphometric analysis of computed tomography images. The most optimal balanced

two prediction models were selected: for the value of the height of the lower edge of the right coronary artery ostia and for the height of the left sinus of Valsalva, which were confirmed by the appropriate reliability criteria. Testing the models proved the correctness of the constructed logical model. Thus, the complex influence of weight (direct) and body mass index (inverse) on the level of the height of the lower edge of the right coronary artery ostia and a strong direct influence of height and weight on the calculations of the height of the left sinus of Valsalva have been established.

Various age-anthropometric dependences on the morphometry of the aorta in different groups of subjects are described. S.Y. Ho describes that the size of the aorta increases with age [5]. X. Wang et al. conducted a study among the Chinese population (3018 patients), excluding individuals with heart valve pathology and probable coronary heart disease, and found that aortic diameters correlated with age in men (p<0.05). Scientists decided to make a correction to the surface area of the body. According to the results of which the correlation with age was again confirmed in men [20]. Dividing the 1286 selected patients into age groups, the researchers found that there was no gender difference in the diameter of the ascending aorta in the group of people under 30 years of age and the group of people over 70 years of age [20].

In the study of T. Plonek et al. [13] describe the lack of correlation between the maximum and minimum diameters of the aortic root and height (r=0.115, p=0.115), weight (r=0.029, p=0.768), body surface area (r=0.079, p=0.426). The lack of correlation with the size of the aorta and the surface area of the body does not coincide with the data of X. Wang et al. [20], P. Nagpal and others. [9], who described it. Concordance between the works of T. Plonek et al. [13], X. Wang and others. [20] about the lack of correlation between the height and the diameter of the ascending aorta, does not coincide with the statement of P. Nagpal et al. [9], who established a correlation between height and the dimensions of the thoracic part of the aorta by measuring it on CT images.

A wide range of diagnostic possibilities, a different approach to measurement, and the heterogeneity of groups in studies lead to the fact that the dimensions and, accordingly, the correlation will differ between populations [4, 6, 17]. Modeling is the next stage. That is why numerous studies are carried out with a focus on the morphometric requirements of manufacturing companies [16, 21], approaching the creation of unified protocols [8, 14], which will make it possible to create models and predict measurements of the studied parameters.

The obtained results create prospects for the implementation and involvement of the proposed models in clinical practice. For Ukraine, radiological research in the anatomical aspect is somewhat new, which requires additional study with the involvement of a larger amount of data.

Conclusion

A model of the height indicator of the left sinus of Valsalva based on height and weight was created; the level of the

height of the lower edge of the right coronary artery ostia from weight and body mass index in healthy men based on computed tomography.

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МОДЕЛЮВАННЯ ПОКАЗНИКІВ ВИСОТИ ПАЗУХ АОРТИ ТА ВІЧОК ВІНЦЕВИХ АРТЕРІЙ В ЗАЛЕЖНОСТІ ВІД ВІКОВО-АНТРОПОМЕТРИЧНИХ ПОКАЗНИКІВ У ЗДОРОВИХ ЧОЛОВІКІВ НА ОСНОВІ КОМП'ЮТЕРНОЇ ТОМОГРАФІЇ**Підеальна У. Є.**

Комп'ютерна томографія є "золотим стандартом" для проведення морфометрії аорти при передопераційних плануваннях в інвазивній кардіології та кардіохірургії. Прогностичне моделювання показників може суттєво зекономити ресурси. Мета дослідження: провести моделювання показників висоти пазух аорти та відходження вічок вінцевих артерій в залежності від віково-антропометричних параметрів у здорових чоловіків на основі комп'ютерної томографії. Матеріал представлений комп'ютерно-томографічними зображеннями аорти та вінцевих артерій з контрастуванням сорока трьох чоловіків за умов норми. Методи: морфометричний та статистичний аналізи. Мультифакторний кореляційно-регресійний аналіз проведено для встановлення комплексного впливу віково-антропометричних параметрів на показники висоти пазух аорти та відходження вічок вінцевих артерій. Достовірність отриманих показників підтверджувалась критерієм Фішера (F). За критерієм автокореляції Дурбіна-Уотсона довели правильність побудованої моделі. У чоловіків в нормі на рівень висоти відходження нижнього краю вічка правої вінцевої артерії суттєво впливали вага (прямий вплив) та індекс маси тіла (зворотний вплив). Коефіцієнт регресії становить $R = +0,632$, при $p < 0,001$, стандартна похибка оцінки (SEE) 2,951. Отримане лінійне рівняння прогностичної моделі: рівень висоти відходження нижнього краю вічка правої вінцевої артерії = $0,359 \times A1 - 1,099 \times A2 + 16,53$. Правильність побудованої моделі перевірено за допомогою критерію автокореляції Дурбіна-Уотсона (2,181). Прогностичну модель розрахунків рівня висоти лівої пазухи аорти формували показники зросту та ваги (сильний прямий вплив): $R = +0,759$, $p < 0,001$, $SEE = 2,208$. Скоригований коефіцієнт множинної детермінації становив $R^2_{adj} = +0,562$. Критерій автокореляції Дурбіна-Уотсона був у межах норми (2,241). Лінійне рівняння прогностичної моделі з отриманими β -коефіцієнтами: рівень висоти лівої пазухи аорти = $35,83 \times A1 + 0,033 \times A2 - 42,22$. Пройдено перевірку роботи прогностичних моделей для різних за антропометричними та віковими параметрами осіб. Таким чином, створено модель залежності показника висоти лівої пазухи аорти від зросту та ваги; рівня висоти відходження нижнього краю вічка правої вінцевої артерії від ваги та індексу маси тіла у здорових чоловіків на основі комп'ютерної томографії.

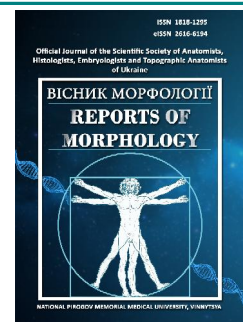
Ключові слова: вічка вінцевих артерій, анатомія, комп'ютерна томографія, аорта.



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Peculiarities of correlations of upper respiratory tract cephalometric parameters in Ukrainian young men and young women regardless of face type

Kostiuchenko-Faifor O. S., Gunas I. V., Glushak A. A., Babych L. V., Skoruk R. V.

National Pirogov Memorial Medical University, Vinnytsia, Ukraine

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CORRESPONDING AUTHOR

e-mail: kostyuchenko.olha.91@gmail.com
Kostiuchenko-Faifor O. S.

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The study of the parameters of the upper respiratory tract has become one of the leading directions of medical research, due to the connection of this structure with the occurrence and course of many diseases of both childhood and adulthood. The study of normative indicators of this structure and its relationship with craniometric indicators should be the first step before further research of samples with pathologies. The purpose of the study is to establish correlations of cephalometric parameters of the upper respiratory tract in Ukrainian young men and young women with an orthognathic bite, regardless of the type of face. Primary lateral radiographs of 49 Ukrainian young men (aged 17 to 21 years) and 76 Ukrainian young women (aged 16 to 20 years) with an orthognathic bite and the absence of upper respiratory tract pathology taken from the database of the research center and the Department of Pediatric Dentistry age of National Pirogov Memorial Medical University, Vinnytsia, with the help of the licensed medical software OnyxCeph^{3™}, version 3DPro (Image Instruments GmbH, Germany) and the diagnostic program "UniqCeph", a cephalometric analysis of the upper respiratory tract was performed. In the "Statistica 6.0" license package, correlations between cephalometric indicators of the upper respiratory tract were assessed using non-parametric Spearman statistics. In Ukrainian young men, multiple, mostly direct, medium-strength (r = from 0.32 to 0.48) and strong (r = from 0.65 to 0.83) correlations were established between most of the characteristics of the upper respiratory tract or tongue; in young women, there are also predominantly direct, medium-strength (r = from 0.33 to 0.57) and strong (r = from 0.62 to 0.85) correlations between most of the characteristics of the upper respiratory tract or tongue, as well as medium-strength inverse (r = -0.30 and -0.40) and direct (r = 0.45 and 0.85) correlations between most characteristics of the soft palate. In addition, in Ukrainian young men, multiple inverse correlations of mainly medium strength (r = from -0.33 to -0.49) were established between the value of the PASmin distance and the UAA section with the value of the SPT distance and the SPA section, and between the value of the NL/PM-U angle and most of the characteristics of the tongue, as well as multiple direct, mostly medium strength (r = from 0.30 to 0.55), connections between the characteristics of the upper respiratory tract itself and the hyoid bone or tongue and between the characteristics of the hyoid bone and the tongue; in young women, there are mainly straight lines of medium strength (r = from 0.33 to 0.55) between the value of the AH-CV distance and most of the characteristics of the upper respiratory tract itself, between the value of the AH-FH distance and all characteristics of the tongue, and between the value of the PM-U distance and by the distance VT and the section TA. Thus, the most pronounced manifestations of sexual dimorphism of connections are established between the characteristics of the soft palate, between the characteristics of the upper respiratory tract itself and the soft palate or tongue, as well as between the characteristics of the soft palate and the hyoid bone.

Keywords: cephalometry, correlations, upper respiratory tract, soft palate, hyoid bone, tongue, Ukrainian young men and women, orthognathic bite, sexual dimorphism.

Introduction

The study of both external and internal craniofacial (in particular, respiratory tract) structures is one of the debatable

issues of clinical medicine. However, as for most clinical sciences, biomedical anthropology is the primary and

fundamental beginning that will allow us to understand the interrelationship of various structures of the human body.

The human face and, in particular, the central craniofacial structures that form it are the result of many years of evolutionary processes. At the same time, the influence of external faciocranial structures on internal ones (and vice versa) is still a subject of scientific debate. The latest data indicate that the dimensional indicators of the respiratory tract are related to the peculiarities of the development of craniofacial indicators, while the peculiarities of the shape of the respiratory tract are formed to a greater extent depending on climatic changes [3]. Indeed, modern genetic studies show that some features of the morphology of the central part of the face (nasal, zygomatic parts) are formed under the influence of environmental temperature, intensity of solar radiation and atmospheric pressure, which is a vivid manifestation of compensatory and adaptive mechanisms in response to certain environmental parameters [7].

At the same time, the internal respiratory tract is a structure that is "more hidden" from external factors, which significantly interacts with its surrounding structures, such as the tongue, hyoid bone, etc. At the same time, such indicators as the size of the tongue, the length of the pharynx and the length of the mandibular plane to the hyoid bone are related to the weight of the human body, and as an example, in the case of obesity, an increase in their parameters causes an increase in the critical pressure on the closure of the pharynx, which is the driver of collapse in case of obstructive sleep apnea [12, 25].

In general, the study of the parameters of the respiratory tract has become the key to understanding the causes of the occurrence, course, and ways of treating various pathologies [20, 22]. This causes intensification of researchers' efforts with the aim of in-depth study of the parameters of these structures and their interaction with other structures.

No less important for understanding the picture as a whole is the analysis of the impact of orthognathic surgical intervention on subsequent changes in airway parameters. The meta-analysis data of 21 publications prove that, regardless of facial features or other patient data, respiratory parameters undergo various changes in their parameters, which do not return to their original values even 6 years after the intervention [8].

Thus, an intervention aimed at rapid expansion of the upper jaw causes an increase in the volume of the nasal cavity and nasopharynx already by 3 months [19]. At the same time, no significant differences were found in the change in the size of the oropharynx when using orthodontic treatment in adults [21].

However, the interpretation of certain results requires a correct understanding of the received radiological data, which requires the use of the correct positioning of the patient, otherwise it causes a distortion of the obtained indicators [15]. In addition, there is a need to obtain normative indicators of cranial indicators and indicators of the respiratory tract,

which would take into account the sex, age and ethnicity of the person. Such work is already being carried out [14], but it is also important to conduct research that would also study the relationships of these elements. The results of such studies on a healthy population of individuals would allow deepening the understanding of the interaction of these structures and thus help medical professionals involved in their treatment.

The purpose of our study is to establish correlations of cephalometric parameters of the upper respiratory tract in Ukrainian young men and young women with an orthognathic bite, regardless of facial type.

Materials and methods

Primary lateral radiographs of 49 Ukrainian young men (YM) (aged 17 to 21 years) and 76 Ukrainian young women (YW) (aged 16 to 20 years) with orthognathic bite and absence of pathology of the upper respiratory tract. All of them underwent a teleröntgenographic (effective radiation dose up to 0.001 mSv) examination using a Veraviewepocs 3D Morita (Japan) dental cone-beam tomograph at the "Vinintermed" private dental clinic.

Committee on Bioethics of National Pirogov Memorial Medical University, Vinnytsya (protocol № 8 From 30.09.2021) found that the studies do not contradict the basic bioethical standards of the Declaration of Helsinki, the Council of Europe Convention on Human Rights and Biomedicine (1977), the relevant WHO regulations and laws of Ukraine.

Cephalometric analysis of the upper respiratory tract was performed using licensed medical software OnyxCeph^{3™}, version 3DPro (company Image Instruments GmbH, Germany) and diagnostic program "UniqCeph" (created in National Pirogov Memorial Medical University, Vinnytsya).

Figure 1 shows *lines used in cephalometric examination*

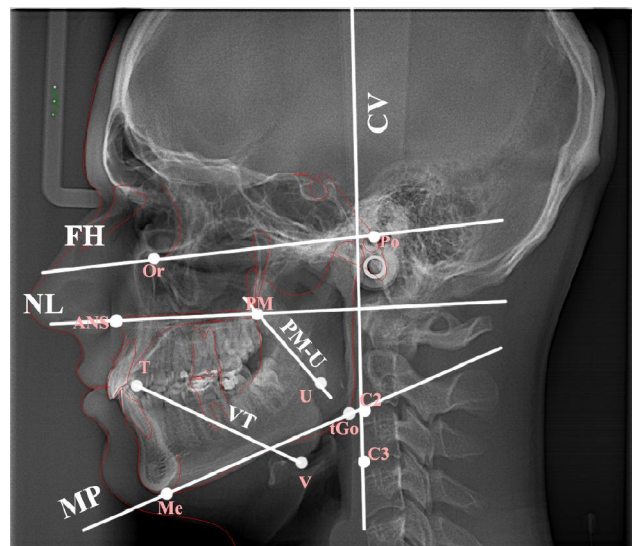


Fig. 1. Cephalometric lines used in cephalometric examination of the upper respiratory tract. CV - cervical plane; FH - Frankfurt plane; MP - mandibular plane; NL - nasal plane; PM-U - longitudinal axis of the soft palate; VT - longitudinal axis of the tongue.

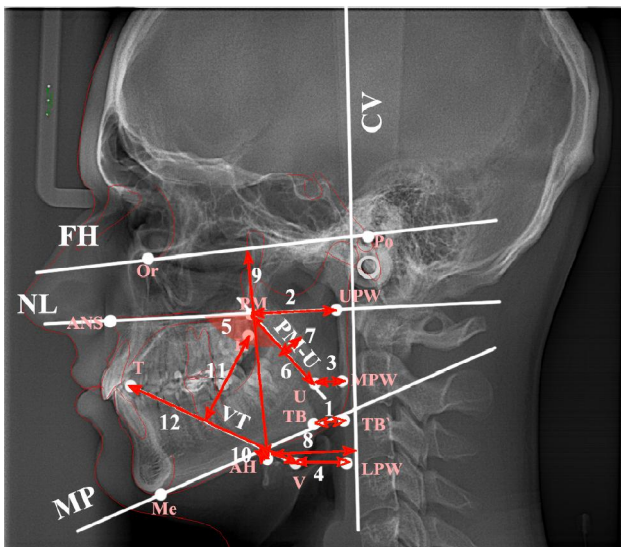


Fig. 2. Cephalometric linear and angular characteristics used in cephalometric examination of the upper respiratory tract. 1 - distance PASmin, 2 - distance PM-UPW, 3 - distance U-MPW, 4 - distance V-LPW, 5 - angle NL/PM-U, 6 - distance PM-U, 7 - distance SPT, 8 - distance AH-CV, 9 - distance AH-FH, 10 - distance AH-MP, 11 - distance H-VT, 12 - distance VT.

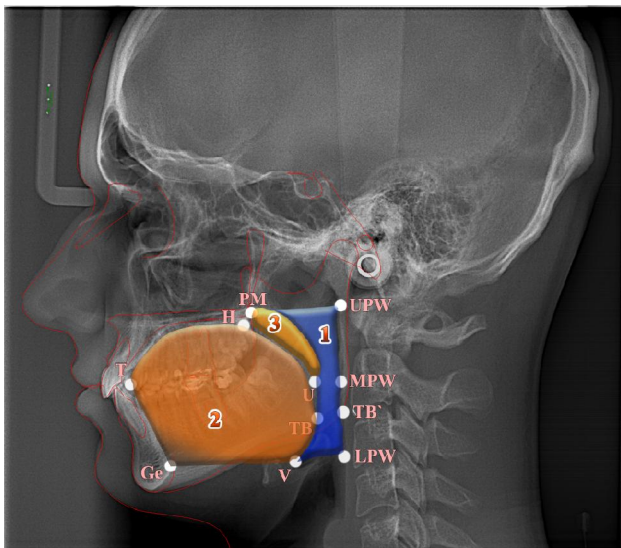


Fig. 3. Cephalometric characteristics of the area used in the cephalometric study of the upper respiratory tract. 1 - area UAA (area of the upper respiratory tract), 2 - area TA (tongue area), 3 - area SPA (soft palate area).

of the upper respiratory tract [23]: plane CV - Cervical plane - passes through points C2 and C3; plane FH - Frankfort plane - passes through points Or and Po; plane MP - Mandibular plane - passes through points Me and tGo; plane NL - Nasal plane - passes through the ANS and PNS points; line PM-U - longitudinal axis of the soft palate - passes through points PM and U; line VT - longitudinal axis of the tongue - passes through points V and T.

Cephalometric indicators used in the cephalometric study of the upper respiratory tract are shown in Figures 2

and 3.

Characteristics of the upper respiratory tract itself:

- distance **PASmin** (also known as Retroglossal oropharyngeal airway space) - distance between points TB and TB` (mm);
- distance **PM-UPW** (also known as Nasopharyngeal airway space) - distance between points PM and UPW (mm);
- distance **U-MPW** (also known as Retropalatal oropharyngeal airway space) - distance between points U and MPW (mm);
- distance **V-LPW** (also known as Hypopharyngeal airway space) - distance between points V and LPW (mm);
- area **UAA** (also known as Upper airway area) - outlined by a contour through the points: PM - UPW - MPW - TB` - LPW - V - PM (mm²).

Characteristics of the soft palate:

- angle **NL/PM-U** (also known as Soft palate inclination Angle) - the angle formed by the lines PM-U and NL (°);
- distance **PM-U** (also known as Soft palate length) - distance between points PM and U (mm);
- distance **SPT** (also known as Maximum soft palate thickness) - the distance between the most distant points perpendicular to the line PM-U (mm);
- area **SPA** (also known as Soft palate area) - outlined by a contour through the points PM and U (mm²).

Characteristics of the hyoid bone:

- distance **AH-CV** (also known as Horizontal position of the hyoid) - distance between points AH and CV (mm);
- distance **AH-FH** (also known as Vertical position of the hyoid with respect to the Frankfort plane) - distance between points AH and FH (mm);
- distance **AH-MP** (also known as Vertical position of the hyoid with respect to the mandible) - distance between points AH and MP (mm).

Characteristics of the tongue:

- distance **H-VT** (also known as Height of the tongue) - distance between points H and VT (mm);
- distance **VT** (also known as Length of the tongue) - distance between points V and T (mm);
- area **TA** (also known as Tongue area) - outlined by a contour through the points T - H - TB - V - Ge - T (mm²).

The assessment of correlations between cephalometric indicators of the upper respiratory tract was carried out in the license package "Statistica 6.0" using non-parametric statistics of Spearman.

Results

Table 1 presents the results of correlations between cephalometric indicators of the upper respiratory tract of Ukrainian YM with an orthognathic bite and the absence of pathology of the upper respiratory tract.

Table 2 presents the results of correlations between cephalometric indicators of the upper respiratory tract of Ukrainian YW with an orthognathic bite and the absence of pathology of the upper respiratory tract.

Table 1. Correlations between cephalometric indicators of the upper respiratory tract in Ukrainian YM (n=49).

	PASmin	PM-UPW	U-MPW	V-LPW	UAA	NL/PM-U	PM-U	SPT	SPA	AH-CV	AH-FH	AH-MP	H-VT	VT
PM-UPW	0.32													
U-MPW	0.72	0.36												
V-LPW	0.76	0.27	0.43											
UAA	0.81	0.48	0.75	0.65										
NL/PM-U	-0.22	-0.34	-0.20	-0.24	-0.12									
PM-U	0.04	-0.02	-0.14	0.16	0.06	0.07								
SPT	-0.43	0.12	-0.23	-0.24	-0.49	-0.14	0.02							
SPA	-0.29	0.10	-0.22	-0.13	-0.37	-0.10	0.46	0.83						
AH-CV	0.52	0.13	0.46	0.55	0.30	-0.29	0.11	-0.01	0.05					
AH-FH	-0.16	-0.23	-0.17	0.02	0.13	0.15	0.15	-0.20	-0.15	-0.21				
AH-MP	-0.01	-0.17	-0.04	0.01	0.25	0.18	0.12	-0.24	-0.14	-0.21	0.68			
H-VT	-0.05	-0.14	-0.25	0.13	0.00	0.13	0.17	-0.16	-0.18	-0.21	0.30	-0.13		
VT	0.34	0.11	0.33	0.24	0.38	-0.38	0.29	-0.07	0.07	0.31	0.17	0.50	-0.28	
TA	0.22	0.15	0.07	0.40	0.33	-0.33	0.40	-0.13	-0.04	0.20	0.18	0.07	0.41	0.47

Notes: here and in the following table, yellow background - reliable weak direct correlations; brown background - reliable medium-strength direct correlations; red background - reliable strong direct correlations; green background - reliable weak feedback correlations; blue background - reliable feedbacks correlations of medium strength.

Table 2. Correlations between cephalometric indicators of the upper respiratory tract in Ukrainian YW (n=76).

	PASmin	PM-UPW	U-MPW	V-LPW	UAA	NL/PM-U	PM-U	SPT	SPA	AH-CV	AH-FH	AH-MP	H-VT	VT
PM-UPW	0.34													
U-MPW	0.57	0.46												
V-LPW	0.69	0.33	0.44											
UAA	0.73	0.54	0.69	0.70										
NL/PM-U	-0.14	-0.42	-0.09	-0.18	-0.10									
PM-U	-0.04	0.22	-0.19	0.12	0.21	-0.18								
SPT	0.16	0.37	0.17	0.02	0.06	-0.30	0.11							
SPA	0.22	0.39	0.06	0.09	0.14	-0.40	0.45	0.85						
AH-CV	0.39	0.17	0.40	0.55	0.37	-0.10	0.08	0.10	0.09					
AH-FH	-0.14	-0.34	-0.20	0.18	0.13	0.19	0.27	-0.28	-0.12	0.12				
AH-MP	0.01	-0.19	0.01	0.16	0.22	0.01	0.25	-0.03	0.03	0.01	0.62			
H-VT	-0.16	-0.10	-0.23	0.12	0.00	0.19	0.15	-0.22	-0.12	0.07	0.42	0.01		
VT	0.14	0.15	0.15	0.13	0.28	-0.48	0.38	0.13	0.33	0.16	0.28	0.45	-0.17	
TA	-0.14	0.03	-0.11	0.18	0.08	-0.21	0.43	-0.04	0.14	0.20	0.37	0.05	0.69	0.29

In the analysis of reliable correlations between the cephalometric characteristics of the upper respiratory tract of Ukrainian YM with an orthognathic bite, multiple direct correlations of medium strength ($r=$ from 0.32 to 0.48) and strong ($r=$ from 0.65 to 0.81) correlations of the PASmin distance and the UAA area with all other cephalometric indicators of the upper respiratory tract, as well as the distances PM-UPW, U-MPW and V-LPW with most of the cephalometric indicators of the upper respiratory tract. The conducted quantitative analysis of reliable correlations between cephalometric characteristics of the upper

respiratory tract itself revealed 9 reliable connections out of 10 possible (90.00 %), of which 40.00 % were direct of medium strength, 50.00 % of direct strong.

In the analysis of reliable correlations between the cephalometric characteristics of the soft palate of Ukrainian YM with an orthognathic bite, the multiple nature and direct correlations were established only between the size of the SPA area and all distances of the soft palate ($r=$ 0.46 and 0.83). The conducted quantitative analysis of reliable correlations between cephalometric characteristics of the soft palate revealed 2 connections out of 6 possible

(33.33 %), of which 16.67 % were direct of medium strength, 16.67 % of direct strong.

When analyzing reliable correlations between the *cephalometric characteristics of the hyoid bone* of Ukrainian YM with an orthognathic bite, only a *direct strong* ($r=0.68$) correlation between the AH-FH and AH-MR distances was established, which is 33.33 % of the 3 possible relationships.

When analyzing reliable correlations between the *cephalometric characteristics of the tongue* of Ukrainian YM with an orthognathic bite, *multiple direct* ($r=0.41$ and 0.47) correlations of the TA area with all tongue distances were established. The conducted *quantitative analysis* of reliable correlations between *cephalometric characteristics of the tongue* revealed 3 connections out of 3 possible (100 %), of which 66.67 % were direct of medium strength, 33.33 % were inverse of weak strength.

In the analysis of reliable correlations between the *cephalometric characteristics of the upper respiratory tract* and the soft palate of Ukrainian YM with an orthognathic bite, *multiple inverse correlations of mostly medium strength* ($r=$ from -0.37 to -0.49) of the PASmin distance and the UAA area with the SPT distance were established and SPA areas. The *quantitative analysis* of reliable correlations between the *cephalometric characteristics of the proper upper respiratory tract and the soft palate* of Ukrainian YM with an orthognathic bite revealed 5 correlations out of 20 possible (25.00 %), of which 5.00 % were inverse of weak strength, 20.00 % were inverse of medium strength.

When analyzing reliable correlations between the *cephalometric characteristics of the upper respiratory tract proper and the hyoid bone* of Ukrainian YM with an orthognathic bite, *multiple straight average strength* ($r=$ from 0.30 to 0.55) correlations were established only between the value of the AH-CV distance and most of the cephalometric characteristics of the upper proper airway respiratory tract. The *quantitative analysis* of reliable correlations between the *cephalometric characteristics of the proper upper respiratory tract and the hyoid bone* of Ukrainian YM with an orthognathic bite revealed 4 connections out of 15 possible (26.67 %), all of which are direct of medium strength.

When analyzing reliable correlations between the *cephalometric characteristics of the proper upper respiratory tract and the tongue* of Ukrainian YM with an orthognathic bite, *multiple direct correlations of medium strength* ($r=$ from 0.33 to 0.40) were established only between the value of the VT distance and more than half of the cephalometric characteristics of the proper upper respiratory tract. The *quantitative analysis* of reliable correlations between the *cephalometric characteristics of the proper upper respiratory tract and the tongue* of Ukrainian YM with an orthognathic bite revealed 5 relationships out of 15 possible (33.33 %), all of which are direct of medium strength.

In the analysis of reliable correlations between the *cephalometric characteristics of the soft palate and hyoid bone* of Ukrainian YM with orthognathic bite, no multiple correlations were established. The *quantitative analysis* of reliable correlations between the *cephalometric characteristics of the soft palate and hyoid bone* of Ukrainian YM with an orthognathic bite revealed only 1 inverse weak strength correlation out of 12 possible (8.33 %).

In the analysis of reliable correlations between the *cephalometric characteristics of the soft palate and the tongue* of Ukrainian YM with an orthognathic bite, *multiple inverse correlations of the average strength* ($r=-0.33$ and -0.38) of the NL/PM-U angle and most tongue characteristics were established, as well as *direct weak and medium strength* ($r=0.29$ and 0.40) correlations between the value of the PM-U distance and most characteristics of the tongue. The *quantitative analysis* of reliable correlations between the *cephalometric characteristics of the soft palate and tongue* of Ukrainian YM with an orthognathic bite revealed 4 connections out of 12 possible (33.33 %), of which 8.33 % were direct of weak strength, 8.33 % were direct of medium strength, and 16.67 % were inverse medium strength.

In the analysis of reliable correlations between the *cephalometric characteristics of the hyoid bone and the tongue* of Ukrainian YM with an orthognathic bite, *multiple direct correlations of medium strength* ($r=0.31$ and 0.50) were established only between the value of the VT distance and most of the cephalometric characteristics of the hyoid bone. The *quantitative analysis* of reliable correlations between the *characteristics of the hyoid bone and the tongue* of Ukrainian YM with an orthognathic bite revealed 3 average direct strength correlations out of 9 possible (33.33 %).

When analyzing reliable correlations between the *cephalometric characteristics of the upper respiratory tract* of Ukrainian YW with an orthognathic bite, *multiple direct relationships of medium strength* ($r=$ from 0.34 to 0.57) and *strong* ($r=$ from 0.69 to 0.73) correlations between all cephalometric indicators were established. The conducted *quantitative analysis* of reliable correlations between the *cephalometric characteristics of the upper respiratory tract itself* revealed 10 connections out of 10 possible (100 %), of which 60.00 % were direct of medium strength, 40.00 % were direct strong.

In the analysis of reliable correlations between the *cephalometric characteristics of the soft palate* of Ukrainian YW with an orthognathic bite, *multiple inverse* ($r=-0.30$ and -0.40) correlations of *average strength* were established between the value of the NL/PM-U angle and the value of the SPT distance and the SPA area, and as well as *medium strength* ($r=0.45$) and *strong* ($r=0.85$) direct correlations between the size of the SPA area and the PM-U and SPT distances. The conducted *quantitative analysis* of reliable correlations between the *cephalometric characteristics of the soft palate* revealed 4 connections out of 6 possible

(66.67 %), of which 16.67 % were direct of average strength, 16.67 % were direct strong, and 33.33 % were inverse of average strength.

When analyzing reliable correlations between the *cephalometric characteristics of the hyoid bone* of Ukrainian YW with an orthognathic bite, as in young men, only a *direct strong* ($r=0.62$) correlation was established between the AH-FH and AH-MR distances, which of the 3 possible correlations is 33.33 %.

In the analysis of reliable correlations between the *cephalometric characteristics of the tongue* of Ukrainian YW with an orthognathic bite, *straight weak* ($r=0.29$) and *strong* ($r=0.69$) correlations of the size of the TA area with all tongue distances were established. The conducted *quantitative analysis* of reliable correlations between *cephalometric characteristics of the tongue* revealed 2 connections out of 3 possible (66.67 %), of which 33.33 % were direct weak and 33.33 % were direct strong.

When analyzing reliable correlations between the *cephalometric characteristics of the proper upper respiratory tract and the soft palate* of Ukrainian YW with an orthognathic bite, *multiple medium-strength direct* ($r=0.37$ and 0.39) and *inverse* ($r=-0.42$) correlations were established between the value of the PM-UPW distance and the magnitude of the SPT distance, the SPA section, and the NL/PM-U angle. The *quantitative analysis* of reliable correlations between the *cephalometric characteristics of the upper respiratory tract proper and the soft palate* of Ukrainian YW with an orthognathic bite revealed 3 correlations out of 20 possible (15.00 %), of which 10.00 % were direct of average strength, 5.00 % were inverse of average strength.

When analyzing reliable correlations between the *cephalometric characteristics of the upper respiratory tract proper and the hyoid bone* of Ukrainian YW with an orthognathic bite, *multiple straight of average strength* (r = from 0.37 to 0.55) correlations were established only between the value of the AH-CV distance and most of the cephalometric characteristics of the upper proper airway respiratory tract. The *quantitative analysis* of reliable correlations between the *cephalometric characteristics of the upper respiratory tract and the hyoid bone* of Ukrainian YW with an orthognathic bite revealed 5 correlations out of 15 possible (33.33 %), of which 26.67 % were direct of average strength, 6.67 % were inverse of average strength.

When analyzing reliable correlations between the *cephalometric characteristics of the proper upper respiratory tract and the tongue* of Ukrainian YW with orthognathic bite, no multiple correlations were established. The conducted *quantitative analysis* of reliable correlations between the *cephalometric characteristics of the upper respiratory tract and the tongue* of Ukrainian YW with an orthognathic bite revealed 2 connections out of 15 possible (13.33 %), of which 6.67 % were direct of weak strength, 6.67 % were reverse of weak strength.

When analyzing reliable correlations between the

cephalometric characteristics of the soft palate and hyoid bone of Ukrainian YW with an orthognathic bite, *multiple weak direct* ($r=0.25$ and 0.27) correlations were established between the value of the PM-U distance and the value of the AH-FH and AH-MP distances. The *quantitative analysis* of reliable correlations between the *cephalometric characteristics of the soft palate and hyoid bone* of Ukrainian YW with an orthognathic bite revealed 3 correlations out of 12 possible (25.00 %), of which 16.67 % were direct of weak strength, 8.33 % were reverse of weak strength.

In the analysis of reliable correlations between the *cephalometric characteristics of the soft palate and tongue* of Ukrainian YW with an orthognathic bite, *multiple direct* ($r=0.38$ and 0.43) correlations between the value of the PM-U distance and the value of the VT distance and the TA area, as well as the average strength of direct ($r=0.33$ and 0.38) and average strength of inverse ($r=-0.48$) correlations between the value of the VT distance and most of the characteristics of the soft palate. The *quantitative analysis* of reliable correlations between the *cephalometric characteristics of the soft palate and tongue* of Ukrainian YW with an orthognathic bite revealed 4 relationships out of 12 possible (33.33 %), of which 25.00 % were direct of average strength, 8.33 % were inverse of average strength.

When analyzing the reliable correlations between the *cephalometric characteristics of the hyoid bone and the tongue* of Ukrainian YW with an orthognathic bite, multiple direct ($r=0.37$ and 0.42) correlations between the AH-FH distance and all characteristics of the tongue were established. The *quantitative analysis* of reliable correlations between the *cephalometric characteristics of the hyoid bone and the tongue* of Ukrainian YW with an orthognathic bite revealed 4 connections out of 9 possible (44.44 %), of which 11.11 % were direct of weak strength, 33.33 % were direct of medium strength.

Discussion

Thus, in Ukrainian YM and YW with an orthognathic bite and the absence of pathology of the upper respiratory tract, when analyzing reliable correlations between the cephalometric indicators of the upper respiratory tract itself, the soft palate, hyoid bone, and the tongue, manifestations of sexual dimorphism of correlations, which are most pronounced between the cephalometric characteristics of the soft palate, between the cephalometric characteristics of the upper respiratory tract proper and the soft palate, between the cephalometric characteristics of the upper respiratory tract proper and the tongue, as well as between the cephalometric characteristics of the soft palate and the hyoid bone.

The results of our research fit quite well into the trends seen in numerous international publications related to the study of the relationships of the upper respiratory tract and cephalometric indicators.

Comparison of cephalometric indicators in individuals of skeletal classes I and II with normal facial types showed

that representatives of class II had smaller values of pharynx volume, airway area, and MCA ($p < 0.01$, $p = 0.03$, and $p = 0.008$, respectively) and a shorter distance U-MS ($p < 0.001$). Airway volume and area have a significant positive correlation with the U-MS distance ($r = 0.22$, $p = 0.005$ and $r = 0.28$, $p < 0.005$ respectively) and a negative correlation with the ANB angle ($r = -0.23$, $p = 0.002$ and $r = -0.21$, $p = 0.007$ respectively) [10].

Comparison of data from individuals of all three skeletal classes shows significant differences in the depth of the lower pharyngeal and nasopharyngeal airways and the area of the soft palate. At the same time, both horizontal and vertical dimensions are larger in men than in women [13].

When evaluating the indicators of the respiratory tract of patients with II skeletal malocclusion class divided into three subgroups, the researchers did not find any significant differences between the subgroups ($p > 0.05$). However, after adding the hyoid bone position assessment parameter, a statistically significant difference between Hy-PG measurements was found ($p < 0.05$) [4]. Taking into account the position of the hyoid bone is indeed an important element in the analysis of respiratory tract indicators. In the next study, when working with patients with class III malocclusion, the authors found significant differences between the studied subgroups for Hy-A, Hy-S, Hy-SN and Hy-FH indicators ($p < 0.05$) [5]. The analysis of the results of our study shows that in individuals with an orthognathic bite there are reliable correlations between the respiratory tract and surrounding structures and cephalometric indicators.

At the same time, the data of some studies show that if we take into account the type of facial growth and the position of the hyoid bone, then there is no statistically significant difference in the studied indicators of the respiratory tract in the various studied groups, except for the PNS-EP indicator, which is significantly shorter in individuals with III skeletal class and hypodivergent face type ($p < 0.05$) [16].

L. V. Claudino et al. [6] carried out a fundamental study on the establishment of normative indicators for each of the departments of the respiratory tract in persons with different types of facial skeletal class. As a result, it was found that individuals with class II had lower minimum and average values of all sections of the respiratory tract than representatives of class III. The most uniform morphology of the respiratory tract is characteristic of persons with the I and III skeletal class of the face.

Consideration of gender is key in the formation of any research samples. Cephalometric analysis of respiratory tract indicators shows the existence of significant differences for T-PPW, ANS-PNS, BA-PNS, APW2-PPW2 and HY-APW2 indicators ($p < 0.05$) [24].

Taking into account the ethnic component in the study of the respiratory tract is mandatory, because the existence of differences in anthropometric indicators within different populations is a proven fact. On the example of the Lebanese population, significant differences were found

in 12 out of 19 analyzed cephalometric indicators. In particular, within the population, manifestations of sexual dimorphism were found for the size of the uvula and tongue, the distance from the back pharyngeal wall of the epiglottis (larger values in men) [9].

It is equally important to take into account the age of the examined persons. The use of lateral cephalograms to measure the morphology of the upper respiratory tract is a fairly sensitive and reliable method, however, at the same time, it is noted that the evaluation of the parameters of the tongue and soft palate has limited reliability [23].

From the point of view of various accompanying pathologies, data on cephalometric indicators of the respiratory tract are also important information. Analysis of data in children with different types of breathing showed that mouth-breathing children had significant differences from nose-breathing children for SNB ($p < 0.036$), NSGN ($p < 0.028$) and posterior face height/total anterior face height ratios ($p < 0.012$) [11].

In the case of obstructive sleep apnea, there is a pronounced relationship between craniofacial disharmony and the presence of this disease. Among such parameters, heterogeneity is particularly evident in relation to ALFH, GO-H, Gogn-H, Gognng-H, PNS-PHW and pharynx area [17].

Domestic studies on the relationship of cranial and other surrounding structures depending on the types of face are single, and so far aimed at studying the relationship with dental and jaw indicators [18].

At the same time, it is worth paying attention to the existence of works that show the influence of the type of face on the parameters of the respiratory tract. In persons with average faces and skeletal class II there was reduced glossopharyngeal airway volume and at the same time there was found that persons with long faces have higher values of nasal minimum constricted area [2].

G. Acharya with co-authors [1] using the analysis of 210 lateral cephalograms according to the McNamara method, they established the average values of the width of the upper and lower respiratory tracts in persons belonging to different skeletal classes and facial shapes, namely 12.07 and 9.51 mm in persons of the I class, 11.57 and 9.13 mm - II class, 12.34 and 10.03 mm - III class and 12.35 and 9.62 mm in mesofacials, 11.83 and 9.34 mm in dolichofacials and 11.81 and 9.61 mm in brachyfacials. The average values were higher in men, which confirms the manifestations of sexual dimorphism that we discovered.

In this regard, it is necessary to carry out further research aimed specifically at studying this interaction, but with the parameters of the respiratory tract and the inclusion of such a parameter as face types in the sample.

Conclusion

1. In Ukrainian YM with an orthognathic bite and the absence of pathology of the upper respiratory tract, multiple mostly direct correlations of medium strength ($r =$ from

0.32 to 0.48) and strong ($r =$ from 0.65 to 0.83) were established between most of the cephalometric characteristics of the upper respiratory tract itself (90.00 %) or tongue (100 %); in YW, there are also mostly direct medium-strength ($r =$ from 0.33 to 0.57) and strong ($r =$ from 0.62 to 0.85) correlations between the majority of cephalometric characteristics of the upper respiratory tract itself (100 %) or the tongue (66.67 %), as well as medium strength inverse ($r = -0.30$ and -0.40) and direct ($r = 0.45$ and 0.85) correlations between most cephalometric characteristics of the soft palate (66.67 %).

2. In Ukrainian YM with an orthognathic bite and the absence of pathology of the upper respiratory tract, multiple inverse correlations of mainly medium strength ($r =$ from -0.33 to -0.49) of the PASmin distance and the UAA area with the SPT distance and the SPA area were established (25.00 %) and between the value of the NL/PM-U angle and most of the characteristics of the tongue (16.67 %), as well as multiple direct, mostly medium-strength ($r =$ from

0.30 to 0.55) correlations between the cephalometric characteristics of the upper respiratory tract itself and the hyoid bone (26.67 %) or tongue (33.33 %) and between the cephalometric characteristics of the hyoid bone and tongue (33.33 %); in YW, there are mostly straight of medium strength ($r =$ from 0.33 to 0.55) correlations between the value of the AH-CV distance and most of the cephalometric characteristics of the upper respiratory tract itself (26.67 %), between the value of the AH-FH distance and all characteristics of the tongue (33.33 %) and between the value of the distance PM-U and the value of the distance VT and the TA section (16.67 %).

3. The most pronounced manifestations of sexual dimorphism of connections are established between the cephalometric characteristics of the soft palate, between the cephalometric characteristics of the upper respiratory tract itself and the soft palate or tongue, as well as between the cephalometric characteristics of the soft palate and the hyoid bone.

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ОСОБЛИВОСТІ КОРЕЛЯЦІЙ ЦЕФАЛОМЕТРИЧНИХ ПАРАМЕТРІВ ВЕРХНІХ ДИХАЛЬНИХ ШЛЯХІВ В УКРАЇНСЬКИХ ЮНАКІВ І ДІВЧАТ БЕЗ УРАХУВАННЯ ТИПУ ОБЛИЧЧЯ

Костюченко-Файфор О. С., Гунас І. В., Глушак А. А., Бабич Л. В., Скорук Р. В.

Дослідження параметрів верхніх дихальних шляхів стало одним з провідних напрямків медичних досліджень, у зв'язку з пов'язаністю даної структури з виникненням та перебігом багатьох захворювань як дитячого, так і дорослого віку. Вивчення нормативних показників даної структури та її зв'язку з краніометричними показниками має бути першим кроком перед подальшим дослідженням вибірок з патологіями. Мета дослідження - встановлення особливостей кореляцій цефалометричних параметрів верхніх дихальних шляхів в українських юнаків і дівчат із ортогнатичним прикусом без урахування типу обличчя. На первинних бокових телерентгенограмах 49 українських юнаків (віком від 17 до 21 років) і 76 українських дівчат (віком від 16 до 20 років) із ортогнатичним прикусом і відсутністю патології верхніх дихальних шляхів, які взяті з бази даних науково-дослідного центру та кафедри стоматології дитячого віку Вінницького національного медичного університету ім. М. І. Пирогова, за допомогою ліцензованого медичного програмного забезпечення *ОпухСерп™*, версії *3DPro* (компанії *Image Instruments GmbH*, Німеччина) та діагностичної програми *"UniqСерп"* проведений цефалометричний аналіз верхніх дихальних шляхів. У ліцензійному пакеті *"Statistica 6.0"* проведено оцінку кореляцій між цефалометричними показниками верхніх дихальних шляхів за допомогою непараметричної статистики Спірмена. В українських юнаків встановлені множинні переважно прямі середньої сили ($r =$ від 0,32 до 0,48) та сильні ($r =$ від 0,65 до 0,83) зв'язки між більшістю характеристик власно верхніх дихальних шляхів або язика; у дівчат - також переважно прямі середньої сили ($r =$ від 0,33 до 0,57) та сильні ($r =$ від 0,62 до 0,85) зв'язки між більшістю характеристик власно верхніх дихальних шляхів або язика, а також середньої сили зворотні ($r = -0,30$ і $-0,40$) та прямі ($r = 0,45$ і $0,85$) зв'язки між більшістю характеристик м'якого піднебіння. Крім того, в українських юнаків встановлені множинні зворотні переважно середньої сили ($r =$ від $-0,33$ до $-0,49$) зв'язки величини відстані *PASmin* і ділянки *UAA* з величиною відстані *SPT* і ділянки *SPA* та між величиною кута *NL/PM-U* та більшістю характеристик язика, а також множинні прямі, переважно середньої сили ($r =$ від 0,30 до 0,55), зв'язки між характеристиками власно верхніх дихальних шляхів і під'язикової кістки або язика та між характеристиками під'язикової кістки та язика; у дівчат - переважно прямі середньої сили ($r =$ від 0,33 до 0,55) зв'язки між величиною відстані *AN-CV* та більшістю характеристик власно верхніх дихальних шляхів, між величиною відстані *AN-FH* й усіма характеристиками язика та між величиною відстані *PM-U* та величиною відстані *VT* і ділянки *TA*. Таким чином, найбільш виражені прояви статевого диморфізму зв'язків встановлені між характеристиками м'якого піднебіння, між характеристиками власно верхніх дихальних шляхів та м'якого піднебіння або язика, а також між характеристиками м'якого піднебіння та під'язикової кістки.

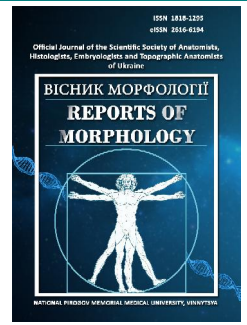
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Adaptive capabilities of the body and aggressive personality manifestations of modern students at various stages of education in a higher education institution

Stoyan N. V.¹, Ocheredko O. M.¹, Korobchanskyi V. O.², Bratkova O. Yu.¹, Serebrennikova O. A.¹

¹National Pirogov Memorial Medical University, Vinnytsya, Ukraine

²Kharkiv National Medical University, Kharkiv, Ukraine

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CORRESPONDING AUTHOR

e-mail: stoyan.nataliya1987@ukr.net

Stoyan N. V.

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The determination of the subsequent comprehensive assessment of the peculiarities of the course of adaptation processes, which are characteristic of modern student youth who acquire a certain profession, are closely related to the establishment of the regularities of the course of numerous adaptive mechanisms in the plane of implementation of psychophysiological, mental, and socio-psychological adaptation. The purpose of the work is to carry out a comprehensive hygienic assessment of the adaptation capabilities of the organism based on the definition of its social and psychological component and aggressive personality manifestations of modern students at various stages of education in a higher education institution. Scientific studies were conducted using questionnaires by Rogers and Diamond and Bass-Darky. 307 students, including 150 young women and 157 young men, who studied in the first, third and sixth years of the medical faculty were under supervision during the observation period. The analysis of the obtained data involved the application of descriptive statistics procedures based on the application of the statistical analysis program package "Statistica 6.1" (license number BXXR901E245722FA). It was established that the highest level of expression of integral indicators of social and psychological adaptation of students, regardless of the time of study in a higher education institution, is characteristic of the characteristics of adaptation manifestations regarding the desire to dominate and accept others; at the same time, the lowest level of expression is for the characteristics of internality and therefore, determines the presence of pronounced signs of transformations of the adaptive content, which mark the tense course of the processes of social and psychological adaptation of students to the conditions of stay in a medical institution of higher education. It was found that among the overwhelming number of students who were studied, the indicators of aggressive personality manifestations exceed the values typical for normative age-sex indicators. This situation determines the need for the development of methods for a comprehensive assessment of the state of adaptive resources of the body of young men and women studying and scientific substantiation of health-preserving technologies, based on which measures of psychohygienic correction should take the leading place.

Keywords: students, institution of higher education, training, personality traits, psychophysiological adaptation, mental adaptation, socio-psychological adaptation, aggressiveness.

Introduction

Determining the peculiarities of the course of adaptation processes typical for student youth who acquire certain professions in today's conditions is closely related to the assessment of the course of a number of adaptive mechanisms, which are mainly in the plane of psychophysiological, mental, and socio-psychological

adaptation [3]. Thus, the course of psychophysiological adaptation is clearly related to ensuring the optimal organization of numerous psychophysiological relationships that take place (primarily in the structures of the central nervous system, visual-sensory and audio-motor systems, coordination of movements, etc.) and

determine the course of preservation processes favorable for the human body somatic and mental health. It should only be noted that the organization of the relationships of the leading psychophysiological functions is carried out thanks to the construction of certain functional systems, which are characterized by both psychological and physiological mechanisms of regulation [23, 25]. Mental adaptation determines the establishment of an optimal relationship between the individual and the environment during the performance of either usual or unusual daily activities, allowing a person to fully satisfy specific needs and implement related tasks while maintaining a high level of somatic and mental health [7, 32, 34]. After all, socio-psychological adaptation is a concrete result of the individual's direct adaptation to the conditions of the environment based on the use of a wide variety of social means through the use of optimal methods of behavior, which, in fact, determine the social status of the individual [15, 16, 17, 18].

It should be noted that recently the problems of psychophysiological and mental adaptation have often been at the center of a number of scientific studies conducted, in particular, by representatives of the Vinnytsia School of Hygiene [30, 31, 32]. On the other hand, questions of formation and development of socio-psychological adaptation, features of its course, consequences of the implementation of individual components have almost never been the subject of a separate scientific study.

In this context, one cannot fail to note the fact that aggressive personality manifestations are extremely closely related to the processes of social and psychological adaptation [35]. The reason for this phenomenon is quite simple. Unsatisfactory social living conditions are one of the leading (even criterion!) factors in the formation of maladaptive manifestations, dissatisfaction with one's existence, and the development of adverse reactions in response. In general, aggressiveness is a certain situational state, which is characterized by affective outbursts of anger and manifestations of impulsive "destructive" behavior directed at the object of frustration, which is the direct cause of the conflict, realized on a cognitive (ensures a person's orientation in the situation), emotional (appears in certain emotional states (anger, hostility, etc.)) and volitional (ensures the achievement of his goal, which is set for himself by an aggressive subject) levels [34].

The purpose of the work is to carry out a comprehensive hygienic assessment of the adaptation capabilities of the organism based on the determination of its social and psychological component and aggressive personality manifestations of modern students at various stages of education in a higher education institution.

Materials and methods

Scientific studies, which involved the implementation of a comprehensive hygienic assessment of the adaptation

capabilities of the body based on the definition of its socio-psychological component and aggressive personality manifestations of modern students, were conducted at various stages of education in a higher education institution. During the observation period, there were 307 students, including 150 young women and 157 young men, who were studying in 1 (50 young women and 56 young men), 3 (50 young women and 51 young men) and 6 (50 young women and 50 young men) courses, respectively.

In order to objectively determine and hygienically assess the features of social-psychological adaptation as one of the most objective indicators of the state of adaptive capabilities of the students' body and the personal traits clearly related to it, the Rogers and Diamond personality questionnaire was used in the course of the research, which provided determination of both its individual correlates and, first of all, established the degree of expression of such integral indicators as indicators of adaptation, self-acceptance, acceptance of others, internality, as well as the desire for dominance [27].

At the same time, in order to determine the level of distribution among student youth of certain personally significant manifestations of aggressive content, the Bass-Darkey personal questionnaire was used, which allowed to determine the most typical forms of aggressive behavior for the studied persons and to establish the degree of their expression in the range from moderate to high according to with such scales as scales of physical, verbal and indirect aggression, negativism, irritability, suspiciousness, "feeling of resentment" and "feeling of guilt". The level of expression of aggressive manifestations was considered moderate if the level of expression of the achieved indicators did not reach 55 points, on the other hand, high if the level of their expression exceeded 55 points [27].

Further analysis of the received data and their subsequent prognostic assessment required the use of descriptive statistics procedures by using the licensed standardized package of statistical analysis application programs "Statistica 6.1" (license number BXXR901E245722FA).

The work is a fragment of the planned research work of the National Pirogov Memorial Medical University, Vinnytsia: "Physiological and hygienic assessment of the peculiarities of adaptation of children, adolescents and young people to the conditions of learning in modern educational institutions and the scientific basis of university hygiene: career guidance aspects, problems of introducing health-preserving technologies and creation of a preventive educational environment" (state registration number 0116U000038). The conducted research fully complies with the basic bioethical norms of the Helsinki Declaration, the Council of Europe Convention on Human Rights and Biomedicine, the relevant provisions of the WHO and the Ministry of Health of Ukraine, as well as the ethical standards established by the Bioethics Committee of the National Pirogov Memorial Medical University, Vinnytsia

(protocol No. 10 of 26.11.2020). All authors have read the text of the manuscript and have given consent for its publication. There is no conflict of interest.

Results

The key to obtaining informative and valid indicators for determining the degree of adaptability of students to the conditions of being in a medical institution of higher education and, first of all, its social and psychological component, is the use of the personal questionnaire of Rogers and Diamond, the work of the researched persons with which allows you to get a well-founded and quite specific idea of the main prerequisites for creating favorable conditions for ensuring the maximum effectiveness of educational and extracurricular activities of girls and boys under the conditions of achieving such a degree of functional mobilization of the personality of individual representatives of student youth that does not cause overstrain and does not contribute to the development of premature fatigue [26, 27, 31]. It should also be noted that the basis of the article is mainly the previously unpublished data obtained in the research [33], which require in-depth interdisciplinary and interdisciplinary professional interpretation and versatile interpretation by specialists of various directions regarding the prospects for their further wide use in medical industry in general.

Thus, in this context, during the psychohygienic assessment of integral indicators of adaptation, which make it possible to identify the generalized degree of adaptation of students to the conditions of optimal interaction with their peers, friends and just those around them in the system of interpersonal relations that has developed, it was found that their significance among young men, who studied in the 1st year, were 0.587 ± 0.012 points, among young women who studied in the 1st year - 0.561 ± 0.013 points, respectively, among young men who studied in the 3rd year - 0.587 ± 0.011 points, respectively ($p > 0.05$), among young women who studied in the 3rd year - respectively 0.623 ± 0.009 points ($p < 0.01$), among young men who studied in the 6th year - respectively 0.608 ± 0.014 points ($p > 0.05$), among young women who studied in the 6th year - respectively 0.613 ± 0.013 points ($p < 0.05$). It is interesting that the level of expression of the studied indicators at the beginning of the training period was higher among young men, in the middle of it - among young women, and at the end - completely leveled off. However, statistically significant differences were observed when comparing data specific to female students of the 1st and 3rd years ($p < 0.01$) and 1st and 6th years ($p < 0.05$). There were no statistically significant sex-related differences ($p > 0.05$).

The results characterizing the peculiarities of the values of integral indicators of self-acceptance, determining the degree of expression of a positive assessment of one's personal qualities, confidence in one's own attractiveness and interest for others as a person, testified to the fact that their level among young men was 0.590 ± 0.014 points in first-year young men and also 0.587 ± 0.010 points in third-

year young men ($p > 0.05$) and slightly increased to 0.613 ± 0.009 points in graduate young men ($p > 0.05$), among first-year young women it was the lowest, amounting to 0.563 ± 0.013 points, increasing significantly in the following period studying at the medical institution up to 0.624 ± 0.012 points ($p < 0.01$) in third-year young women and to a certain extent decreasing to 0.609 ± 0.013 points ($p > 0.05$) in female graduates. It is interesting that, as in the previous case, the level of expression of the investigated indicators at the beginning of the training period was higher among young men, in the middle of it - among young women, and at the end - completely unambiguous values were registered. Statistically significant discrepancies were observed when comparing the data characteristic of female students of the 1st and 3rd years ($p < 0.01$). There were no statistically significant sex-related differences ($p > 0.05$).

The data related to another component of the leading indicators of social and psychological adaptation of students, namely, indicators regarding the evaluation of the features of the integral indicators of acceptance of others, establishing a certain degree of tolerance to other people, and above all, to their shortcomings, negative traits and actions, were characterized by the following characteristics. Thus, their values among young men who studied in the 1st year were 0.633 ± 0.011 points, among young women who studied in the 1st year - respectively 0.594 ± 0.009 points, among young men who studied in the 3rd year - respectively 0.622 ± 0.008 points ($p > 0.05$), among young women who studied in the 3rd year - respectively 0.644 ± 0.011 points ($p < 0.001$), among young men who studied in the 6th year - respectively 0.658 ± 0.010 points ($p > 0.05$), among young women, who studied in the 6th year - respectively 0.659 ± 0.008 points ($p > 0.05$). As in the two previous cases, the level of expression of the studied indicators at the beginning of the training period was higher in young men, in the middle of it - in young women, and at the end - the same level was registered according to the degree of expression of the value. However, statistically significant differences were observed when comparing the data characteristic of female students of the 1st and 3rd years ($p < 0.001$). Statistically significant sex-related differences were characteristic only for young men and young women studying in the 1st year ($p < 0.05$).

Considering the features of the leading personal adaptation-significant manifestations from the side of integral indicators of emotional comfort, which, first of all, determine the degree of emotionally colored feeling of satisfaction with the surrounding reality, it should be noted that their level among young men was 0.578 ± 0.012 points in first-year young men and also 0.590 ± 0.011 points in third-year young men ($p > 0.05$) and increased to 0.613 ± 0.013 points in graduate young men ($p > 0.05$), among first-year young women - 0.558 ± 0.009 points, significantly increasing during the next period of stay at the medical institution, up to 0.623 ± 0.012 points ($p < 0.01$) in third-year young men and slightly decreasing to 0.614 ± 0.014 points ($p < 0.05$) in female graduates. The level of expression of the studied indicators

at the beginning of the training period was higher among young men, in the middle of it - among young women, and at the end - equivalent values were recorded. Statistically significant discrepancies were observed when comparing data specific to female students of the 1st and 3rd years ($p < 0.01$) and 1st and 6th years ($p < 0.05$). There were no statistically significant sex-related differences ($p > 0.05$).

The results of determining the integral indicators of internality, which indicate the level of superiority of internal motivation over external stimuli and exercise control over one's own actions, testified to the fact that their values among young men who studied in the 1st year were 0.517 ± 0.011 points, among young women who studied in 1st year - respectively 0.488 ± 0.010 points, among young men who studied in the 3rd year - respectively 0.508 ± 0.010 points ($p > 0.05$), among young women who studied in the 3rd year - respectively 0.536 ± 0.014 points ($p < 0.01$), among young men who studied in the 6th year - respectively 0.542 ± 0.012 points ($p > 0.05$), among young women who studied in the 6th year - respectively 0.543 ± 0.012 points ($p > 0.05$). It is important to note the fact that, as in the two previous cases, the level of expression of the studied indicators at the beginning of the training period was higher among young men, in the middle of it - among young women, and at the end - the same was recorded according to the degree of expression of the value. However, no statistically significant differences were observed, nor were there any statistically significant sex-related differences ($p > 0.05$).

In the end, the data regarding the assessment of the features of the integral indicators of the desire for dominance, which establish the degree of expression of the ability to influence others, to defend one's own opinion and one's own position, testified to the fact that their level among young men was 0.740 ± 0.012 points in 1st year young men and also 0.740 ± 0.012 points in third-year young men ($p > 0.05$) and 0.754 ± 0.012 points in young graduates ($p > 0.05$), among first-year young women it was 0.700 ± 0.012 points, significantly increasing during the next period of stay in a medical institution higher education up to 0.763 ± 0.013 points ($p < 0.01$) in third-year young women and slightly decreasing to 0.762 ± 0.089 points ($p < 0.05$) in graduate young women. The level of expression of the investigated indicators at the beginning of the training period was higher among young men, in the middle and at the end - among young women. Statistically significant discrepancies were observed when comparing data specific to female students of the 1st and 3rd years ($p < 0.01$) and 1st and 6th years ($p < 0.05$). Statistically significant sex-related differences were characteristic only for young men and young women studying in the 1st year ($p < 0.05$).

The high level of sincerity of the answers of young women and young men was confirmed by the data on the assessment of the degree of expression of the indicated indicators among students of different courses, which in the dominant number of cases corresponded to the level of average values and was mainly manifested as answers

that should be classified as absolutely frank and frank and only in 8.5-10.0 % of cases of situational frank answers.

Generalized data on the peculiarities of the expression of integral indicators of socio-psychological adaptation of male and female students during the period of obtaining higher education are shown in Figure 1.

An important place in the structure of personal manifestations of student youth, which determine their motivation to carry out certain actions and the implementation of certain behavioral decisions, is occupied by aggressiveness, which is a personality trait, the main feature of which is the presence of pronounced destructive tendencies, and the main personal manifestations: conflict, hostility, lack of necessary respect for others, a pronounced oppositional view of the events taking place, etc. [23, 26, 31].

In the course of research conducted on the basis of the application of the personal questionnaire of Bass-Darkey, which made it possible to determine the forms of aggressive behavior typical for modern students of various courses of a medical institution of higher education and to establish the degree of their expression in a sufficiently large range from low and moderate to elevated and high in accordance with 8 basic scales.

In general, and this fact should be noted as the first when performing a psychohygienic assessment of the characteristics of aggressive manifestations of personal genesis, the level of expression of various forms of aggression that take place in the student environment is quite high, thereby testifying to a significant degree of spread of various forms of aggressive in nature behavioral actions and deeds.

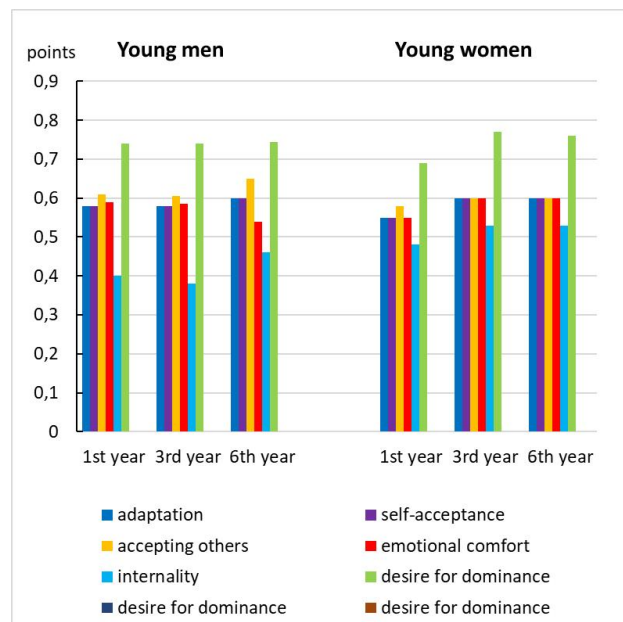


Fig. 1. Integral indicators of social and psychological adaptation of young men and women studying in the conditions of a modern institution of higher medical education according to the personal questionnaire of Rogers and Diamond.

At the same time, considering the level of development of individual manifestations of aggressiveness of the studied students, it was necessary to note that one of the least developed in comparison with other types of aggressive manifestations should be considered indicators on the scale of physical aggression, which reflected the tendency to direct use of physical force by one person against another during the resolution of conflict situations. Thus, the level of the studied indicators among 1st year young men was 43.56 ± 2.68 points, among 1st year young women - 53.82 ± 2.88 points. Somewhat different data were recorded among third-year young men and third-year young women - the level of indicators of physical aggression among them was 55.66 ± 3.41 points ($p < 0.05$) and 47.00 ± 3.22 points ($p > 0.05$), respectively. Almost similar indicators were registered among graduate students - the level of expression of indicators of physical aggression among them was 57.62 ± 3.15 points ($p < 0.001$) in young men and 49.72 ± 2.45 points ($p > 0.05$) in young women. However, statistically significant differences were observed only in case of comparison of data specific to young students of the 1st and 3rd years ($p < 0.05$) and for young students of the 1st and 6th years ($p < 0.001$). Significant sex-related differences were registered only among young men and young women who studied in the 1st year ($p < 0.05$).

It was necessary to consider the level of development of aggressive manifestations among modern students on the scale of verbal aggression to be sufficiently high, which, first of all, consists in an effort to preferentially reveal negative feelings not through actions, but through the form of verbal appeals (quarrels, conversations in raised tones, etc.) to other people. Thus, among young men and young women studying in the 1st year, their values were 47.24 ± 2.06 points and 46.28 ± 2.31 points, respectively, increasing later in both cases to the highest values by the degree of development and amounting to 62.82 ± 0.37 points, respectively ($p < 0.001$) and 61.45 ± 2.49 points ($p < 0.001$) among young men and young women studying in the 3rd year, and slightly decreasing to the level of 55.04 ± 3.08 points ($p > 0.05$) and 45.92 ± 1.86 points ($p < 0.05$) among young men and young women, who studied in the 6th year. Statistically significant differences between the determined indicators were typical for female students of the 1st and 3rd years ($p < 0.001$), as well as for young students of the 1st, 3rd and 6th years ($p < 0.001$ and $p < 0.05$). Sex-related differences in the studied indicators were observed only between the indicators of young men and young women of 6th year students ($p < 0.05$).

The indicators reflecting the degree of expression of aggressive manifestations on the scale of indirect aggression, which attests to the level of spread of negative feelings of an aggressive content through the implementation of indirect actions directed against other persons, should be considered extremely high, and at the same time having a pronounced upward trend. So, among first-year young men and first-year young women, the level

of the studied indicators was 56.16 ± 2.58 points and 66.85 ± 2.46 points, respectively, among third-year young men and third-year young women - it was 66.98 ± 2.69 points ($p < 0.01$) and 66.90 ± 2.46 points, respectively ($p > 0.05$), among young men graduates and young women graduates, it was 64.36 ± 3.12 points ($p < 0.05$) and 60.58 ± 2.79 points ($p > 0.05$), respectively. Statistically significant differences were observed only in the case of comparison of data specific to young students of the 1st and 3rd years ($p < 0.01$) and young students of the 1st and 6th years ($p < 0.05$). Sex-related differences in the studied indicators were recorded between the indicators of young men and young women students of the 1st year ($p < 0.01$).

The degree of expression of the indicators that determined the level of spread in the personality structure of aggressive manifestations on the scale of negativism, the leading manifestations of which should include oppositional forms of behavior, should also be considered quite significant. Among young men and young women who studied in the 1st year, the values of the indicators of negativism were 47.20 ± 3.73 points and 54.14 ± 3.05 points, among young men and young women who studied in the 3rd year - 54.74 ± 3.44 points ($p > 0.05$) and 58.21 ± 3.86 , respectively points ($p > 0.05$), among young men and young women who studied in the 6th year - 59.72 ± 3.25 points ($p < 0.05$) and 50.92 ± 1.98 points ($p > 0.05$), respectively. Statistically significant differences in the values of the determined indicators were observed only between the indicators of 1st year and graduates ($p < 0.05$). Sex differences were registered only among young men and young women studying in the 6th year ($p < 0.05$).

Indicators that determined the level of spread of aggressive manifestations on the scale of irritability, i.e. the tendency to quickly develop irritable reactions in case of the slightest excitement, initially increased during the observation period, and then gradually decreased. Thus, its indicators in first-year young men were 39.90 ± 2.40 points ($p < 0.001$), in first-year young women - 41.78 ± 2.32 points, in third-year young men - 49.78 ± 2.57 points ($p < 0.001$), in third-year young women 49.68 ± 2.46 points ($p < 0.05$), in male graduates - 46.08 ± 2.71 points ($p < 0.05$), in female graduates - 41.40 ± 2.53 points ($p < 0.05$). Statistically significant differences were registered when comparing indicators among young men who studied in the 1st and 3rd year ($p < 0.001$) and 1st and 6th year ($p < 0.05$), as well as among young women who studied in the 1st and 3rd year ($p < 0.05$) and 3rd and 6th years ($p < 0.05$). There were no significant sex differences ($p > 0.05$).

During the psychohygienic assessment of the features of dynamic changes in indicators that determined the level of spread of aggressive manifestations on the scale of suspicion, the distinctive features of which should be considered a tendency to mistrust in relations with others. Thus, its values were 45.36 ± 2.83 points and 42.83 ± 1.91 points among young men and young women who studied in the 1st year, 46.68 ± 2.73 points ($p > 0.05$) and 52.66 ± 3.24

points ($p < 0.01$) among young men and young women who studied in the 3rd year, as well as 48.10 ± 2.73 points ($p > 0.05$) and 44.66 ± 2.27 points ($p < 0.05$) among young men and young women who studied in the 6th year. Statistically significant differences were observed when comparing the indicators of young women who studied in the 1st and 3rd years ($p < 0.01$), as well as young women who studied in the 3rd and 6th years ($p < 0.05$). On the other hand, there were no sex-related ($p > 0.05$) differences between the values of the studied indicators.

Extremely interesting and, in accordance with the content, completely opposite results were obtained during the study of indicators of aggressiveness on the scales "feeling of resentment" and "feeling of guilt". High levels of feelings of resentment indicate the development of envy of others' successes and rejection of others, on the other hand, high levels of "guilt" indicators determine the conscious judgment of the researched persons that they are the cause of numerous negative, conflict situations.

Considering the indicators on the "feeling of resentment" scale, it should be noted that the degree of their manifestation among young men and young women who studied in the 1st year was 54.08 ± 2.47 points ($p > 0.05$) and 46.19 ± 2.68 points ($p > 0.05$), respectively, among young men and young women who studied in the 3rd year - increased to 55.26 ± 3.81 points ($p > 0.05$) and 54.01 ± 2.98 points ($p > 0.05$), respectively, among young men and young women who studied in the 6th year - decreased to 46.66 ± 3.12 points ($p > 0.05$) and 43.98 ± 3.50 points ($p < 0.05$). Statistically significant differences were observed only in the case of comparison of indicators typical for young students of the 1st and 6th years ($p < 0.05$). Sex-related differences in the studied indicators were registered between the indicators of young men and young women of 1st-year students ($p < 0.05$).

Indicators reflecting the degree of expression of aggressive personality traits on the "feeling of guilt" scale were significantly higher, with pronounced upward trends during the first years of study at a medical institution of higher education. In first-year young men, their level was 62.48 ± 2.48 points, in first-year young women - 48.91 ± 2.59 points, in third-year young men - it increased to 58.26 ± 3.35 points ($p > 0.05$), in third-year young women - to 67.11 ± 2.11 points ($p < 0.001$), in young men graduates it decreased to 56.98 ± 2.80 points ($p > 0.05$), in young women graduates it decreased to 43.78 ± 2.87 points ($p > 0.05$). Statistically significant differences in the determined indicators were observed only in young women who studied in the 1st and 3rd courses ($p < 0.001$). Sex-related differences in the studied indicators were typical for young men and young women of all studied groups ($p < 0.001$).

Figures 2 and 3 present the data of a generalized analysis of the characteristics of indicators of aggressive personality manifestations of students during their stay in a medical institution of higher education.

Indicators such as the index of aggressiveness and

the index of hostility are considered integral values of the degree of expression of aggressive personality traits that were studied. If the index of aggressiveness provides an opportunity to carry out a comprehensive assessment of manifestations of physical and verbal aggression and irritability, then the index of hostility is a comprehensive assessment of manifestations of suspicion and "feeling of resentment". Considering the peculiarities of their distribution in the structure of aggressive manifestations according to the values of the aggressiveness index, it was

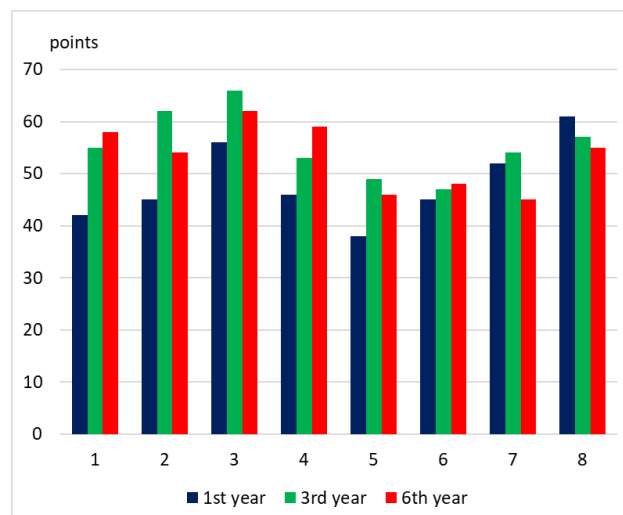


Fig. 2. Indicators of aggressive personality manifestations of young men during the period of study at a medical institution of higher education according to the Bass-Darky personality questionnaire. Notes: 1 - physical aggression; 2 - verbal aggression; 3 - indirect aggression; 4 - negativism; 5 - irritability; 6 - suspiciousness; 7 - feeling of resentment; 8 - feeling of guilt.

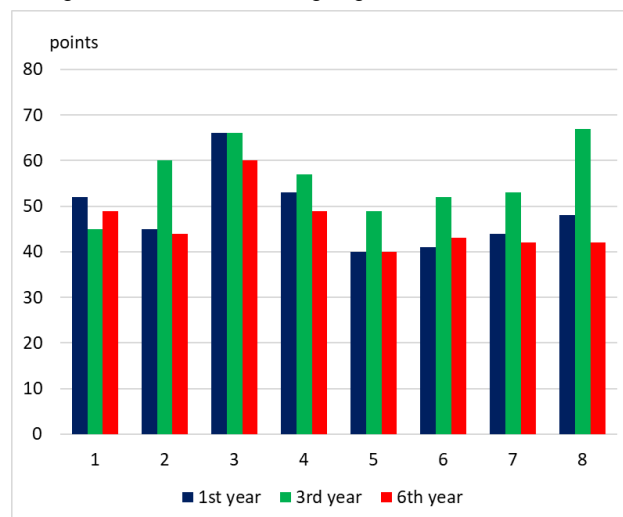


Fig. 3. Indicators of aggressive personality manifestations of young women during the period of study at a medical institution of higher education according to the Bass-Darky personality questionnaire. Notes: 1 - physical aggression; 2 - verbal aggression; 3 - indirect aggression; 4 - negativism; 5 - irritability; 6 - suspiciousness; 7 - feeling of resentment; 8 - feeling of guilt.

necessary to note a significant advantage, especially in the middle and at the end of the period of obtaining higher education, which are high according to the degree of expression of the indicators. Their specific weight among first-year young men and first-year young women was 44.0 % and 57.2 %, among third-year young men and third-year young women - 76.0 % and 66.7 %, respectively, among young graduates and female graduates - 72.0 % and 56.0 %, respectively. At the same time, the share of indicators that indicated a moderate level of development of the studied indicators was 56.0 % and 42.8 % among young men and young women who studied in the 1st year, 24.0 % and 33.3 % among young men and young women who studied in the 3rd year, as well as 28.0 % and 46.0 % among young men and young women who studied in the 6th year.

The data of the analysis of the features of the distribution of indicators of the hostility index both among young women and among young men also testified to the fact that their structure was dominated by the specific weight of values typical for a high level, the value of which was 80.0 % among 1 year young men and 66.1 % among 1 year young women, 76.0 % among third-year young men and 84.3 % among third-year young women, 68.0 % among male graduates and 64.0 % among female graduates. The specific weight of average normative indicators was, respectively, 20.0 % and 33.9 % among young men and young women who studied in the 1st year, 24.0 % and 15.7 % among young men and young women who studied in the 3rd year, and 32.05 and 36.0 % among young men and young women who studied in the 6th year.

Discussion

In medical and psychological research, socio-psychological adaptation is usually considered as the result of a person's adaptation to a certain social environment, which determines the peculiarities of interaction with it [1, 29]. A practically similar approach is characteristic of preventive medicine, according to which socio-psychological adaptation is a concrete result of direct adaptation of an individual to the conditions of the environment based on the use of a wide variety of social means by implementing optimal ways of behavior, which, in fact, determine the social status of the individual [30, 31, 32].

Therefore, based on these positions, adaptation in general and socio-psychological adaptation in particular constitute the process of adaptation of the organism to the demands of the external environment or changes occurring in the organism [2, 11, 12, 22]. Moreover, the too wide interest in the problem of human adaptation indicates the multifaceted nature of adaptive phenomena, which, according to their meaning, take place and, therefore, should be considered from an interdisciplinary perspective as a multi-level phenomenon of a complex biological, physiological, mental and social nature [4, 5, 8, 21]. In fact, adaptation is a complex multifactorial phenomenon that has

its own mechanisms and regularities, which are studied by representatives of many branches of science [13, 14, 20, 24]. Therefore, according to professional interests, scientists focus on certain types of adaptation: biological, mental, psychophysiological, social-psychological, pedagogical, professional, etc. [9, 10, 19]. Moreover, defining the essence of the concept of "adaptation", researchers proceed from the understanding that it (and above all, social-psychological adaptation) should be considered as a process, state, property or result of activity that occurs under certain conditions and lasts for a certain period, as long as dynamic equilibrium will not be established between systems that adapt [6, 24, 28].

In the course of the conducted research, it was established that in the structure of the leading features of the socio-psychological adaptation of modern students of medical institutions of higher education, which were determined, such characteristics as the desire to dominate (the first place in the rating) and the acceptance of others (the second place in the rating), on the other hand, internality characteristics are the lowest (the last sixth place in the rating). At the same time, the data on integral indicators of adaptation, self-acceptance and emotional comfort, which are essential for the successful acquisition of a future profession, occupied an intermediate position [33]. Such results to a certain extent coincided with the data typical for high school students [23]. However, the level of expression of the first two indicators was somewhat higher. Expressed sex-specific features were not registered either.

In the end, it was impossible not to note that the phenomena that were registered testified to a sufficiently intense course of adaptation processes of a social and psychological content, which is very important, based on the fact that social and psychological adaptation is the adaptation of a specific person to the conditions of existence in a group and in establishing certain relationships with its representatives, developing one's own, completely unique style of behavior. Moreover, this applies to almost all forms of adaptive transformations characteristic of socio-psychological adaptation, namely formal (cognitive and informational adaptation to the new environment, new requirements and responsibilities), social (the process of internal integration (unification) of groups and the integration of these groups as a whole) and didactic (student preparation for new forms and methods of educational work of an educational institution) adaptation [3]. Thus, the time spent in a higher education institution is quite closely related to the breaking of former stereotypes, can cause low academic performance and difficulties in communication, contribute to the formation of a whole range of negative experiences associated with the lack of mutual help and moral support, and lead to a significant the expression of aggressive manifestations of personality and the formation of a whole series of manifestations of depressive content [5, 19, 20].

This fact was confirmed by the results of the conducted

research. Thus, during the assessment of the features of aggressive personality manifestations, first of all, it should be noted that the levels of development of various forms of aggression according to the studied scales exceeded the values of values typical for the average normative indicators of representatives of student age and, therefore, for a significant number of young men and women, typical sufficiently expressed various personal manifestations of aggressive content should have been recognized [33]. In particular, the highest values regarding the degree of development of aggressive personality manifestations were characteristic of third-year young men and third-year young women (it was during this period of student life that the highest results were recorded on the scales of indirect and verbal aggression, "feeling of guilt", physical aggression and "feeling of resentment" in young men, according to the scales of "guilt", indirect and verbal aggression, negativism and "feeling of resentment" in young women. At the same time, among first-year young men and first-year young women, the maximum results in terms of expression were characteristic for indicators of aggressiveness according to the scales "feelings of guilt", indirect aggression, "feeling of resentment", verbal aggression and negativism - in the first case, according to the scales of indirect aggression, negativism, physical aggression, "guilt" and verbal aggression - in the second, on the other hand, among young graduates and young women graduates, the maximum results in terms of the degree of expression were typical for indicators of aggressiveness according to the scales of indirect aggression, negativism, physical aggression, "guilt" and verbal aggression - in the former, according to the scales of indirect aggression, negativism, physical aggression, verbal aggression and suspicion - in the latter.

The fact that, among young men, the lowest level of expression of indicators regarding the degree of development of certain forms of aggressive manifestations was mostly characteristic of first-year students and female graduate students, i.e. opposite trends in terms of content were registered as very interesting [33]. In the end, it should be noted that the lowest indicators in terms of degree of expression in the vast majority, regardless of the period of study at a medical institution of higher education, were registered during the analysis of data that proved the level of expression and the degree of spread of the leading characteristics of aggressive manifestations on the scales of irritability and suspicion.

The data obtained, in the future, on the basis of the interdisciplinary and interdisciplinary professional interpretation and versatile interpretation of specialists of various directions, can be used for the development of methods for the comprehensive assessment of the state of adaptive resources of the students' body and the scientific justification of health-preserving technologies that have significant prospects for effective application in the practical activity of medical institutions of higher education.

Conclusion

1. The highest level of expression of integral indicators of socio-psychological adaptation was characteristic of the characteristics of striving for dominance (first place in the rating) and acceptance of others (second place in the rating), the lowest - for the characteristics of internality (the last sixth place in the rating). The characteristics of integral indicators of adaptation, self-acceptance and emotional comfort occupied an intermediate position. Similar trends were typical for male and female students of different courses. The phenomena that were registered testified to the most intense course of adaptation processes of social and psychological adaptation of students to the conditions of stay in medical institutions of higher education.

2. The levels of development of various forms of aggression according to the studied scales exceeded the values typical for average normative indicators and, therefore, a significant number of representatives of student youth had sufficiently expressed various personal manifestations of aggressive content.

3. The highest values regarding the degree of development of aggressive personality manifestations were typical for young men and young women who studied in the 3rd year - it was at this time that the highest results were recorded, first of all, on the scales of indirect and verbal aggression, "feeling of guilt", physical aggression and "feeling of resentment" among young men and on the scales of "feeling of guilt", indirect and verbal aggression, negativism and "feeling of resentment" among young women. At the same time, among young men and young women who studied in the 1st year, the maximum results in terms of the degree of expression were typical for indicators of aggressiveness according to the scales of "guilt", indirect and verbal aggression, "feeling of resentment" and negativism - among the first, and according to the scales of indirect aggression, negativism, physical aggression, "guilt" and verbal aggression - among others, at the same time, among young men and young women who studied in the 6th year, the maximum results in terms of the degree of expression were typical for indicators of aggressiveness on the scales of indirect aggression, negativism, physical aggression A, "guilt" and verbal aggression - among the first, and according to the scales of indirect aggression, negativism, physical and verbal aggression and suspicion - among the second.

4. In young men, the lowest level of expression of indicators regarding the degree of development of individual forms of aggressive manifestations was mostly characteristic of first-year students and female graduate students, i.e. opposite trends in content were registered. The lowest indicators in terms of the degree of expression in the vast majority, regardless of the period of study at the institution of higher education, were registered during the analysis of data that proved the level of expression of the leading characteristics of aggressive manifestations. on the scales of irritability and suspicion.

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ОСОБЛИВОСТІ АДАПТАЦІЙНИХ МОЖЛИВОСТЕЙ ОРГАНІЗМУ ТА АГРЕСИВНИХ ПРОЯВІВ ОСОБИСТОСТІ СУЧАСНИХ СТУДЕНТІВ НА РІЗНИХ ЕТАПАХ НАВЧАННЯ У ЗАКЛАДІ ВИЩОЇ ОСВІТИ

Стоян Н. В., Очерedyкo О. М., Коробчанський В. О., Браткова О. Ю., Сereбреннікова О. А.

Визначення комплексної оцінки особливостей перебігу адаптаційних процесів, котрі властиві для сучасної студентської молоді, що здобуває певний фах, тісно пов'язані зі встановленням закономірностей перебігу численних пристосувальних механізмів у площині реалізації психофізіологічної, психічної та соціально-психологічної адаптації. Метою роботи є здійснення комплексної гігієнічної оцінки особливостей адаптаційних можливостей організму на підставі визначення її соціально-психологічної складової та агресивних проявів особистості сучасних студентів на різних етапах навчання у закладі вищої освіти. Наукові дослідження проводили з використанням опитувальників Роджерса і Даймонда та Басса-Дарки. Під наглядом впродовж періоду спостережень знаходились 307 студентів, в тому числі 150 дівчат і 157 юнаків, які навчались на першому, третьому та шостому курсах медичного факультету. Аналіз отриманих даних передбачав застосування процедур описової статистики на підставі застосування пакету програм статистичного аналізу "Statistica 6.1" (ліцензійний № ВХХR901E245722FA). Встановлено, що найвищий рівень вираження інтегральних показників соціально-психологічної адаптації студентів, незалежно від часу навчання у закладі вищої освіти, властивий для характеристик адаптаційних проявів щодо прагнення до домінування та прийняття інших; разом із тим, найнижчий рівень вираження - для характеристик інтернальності і, отже, визначає наявність виражених ознак перетворень пристосувального змісту, які відзначають напружений перебіг процесів соціально-психологічної адаптації студентів до умов перебування у медичному закладі вищої освіти. Виявлено, що серед переважної кількості студентів, які досліджувались, показники агресивних проявів особистості перевищують значення, властиві для нормативних віково-статевих показників. Таке становище визначає потребу у розробленні методик комплексної оцінки стану адаптаційних ресурсів організму юнаків і дівчат, що навчаються, та наукового обґрунтування здоров'язберігаючих технологій, в основі яких провідне місце мають займати заходи психогігієнічної корекції.

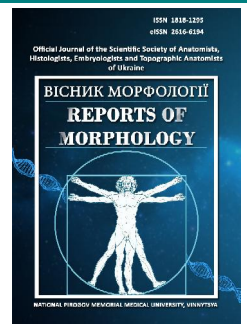
Ключові слова: студенти, заклад вищої освіти, навчання, особливості особистості, психофізіологічна адаптація, психічна адаптація, соціально-психологічна адаптація, агресивність.



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Morphometric analysis of lungs parameters under conditions of simulated burn injury

Lykhatskyi P. H., Ohinska N. V., Getmanyuk I. B., Nebesna Z. M., Trach Rosolovska S. V.

Ivan Horbachevsky Ternopil National Medical University, Ternopil, Ukraine

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CORRESPONDING AUTHOR

e-mail: ohinska@tdmu.edu.ua
Ohinska N. V.

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Thermal burns are one of the most traumatic and physically exhausting injuries. Among the many factors that are decisive for a burn injury, the relationship between the temperature of the damaging agent and the duration of exposure is important. The term of exposure and high temperature determine the depth of the lesion. During burns, hypoxic, hemodynamic and metabolic disorders occur, which lead to changes in the structures and functions of internal organs. There are various ways of developing the respiratory system disorders after a burn injury to the skin: direct thermal damage to the respiratory tract, damage to the lungs by toxins of endogenous origin. After thermal exposure, there is a reorganization of the airiness of the lung tissue, its increase and combination with the phenomena of bronchospasm. A complex of morphological changes develops in the lungs, which includes degenerative changes in the walls of blood vessels and their permeability, a violation of the typical structure of the alveoli, the appearance of foci of disteclases and atelectasis, signs of inflammatory reactions, as well as the detection of areas of clusters of alveolar macrophages in places of hemorrhages. The aim of our study was to establish changes in the morphometric parameters of the lungs during experimental thermal injury to the skin. The results of the morphometric analysis showed that in the early stages (1st, 7th days) after experimental thermal injury to the skin, there is a reorganization of the structural components of the lungs with signs of an adaptive and compensatory nature, as well as destructive changes. It was established that the average values of the area of bronchi, lymphoid tissue statistically significantly increased from the indicators of the intact group animals, while the percentage of unchanged lung tissue significantly decreased in the respiratory portion. It was found that in the late stages of the experiment (14th, 21st days), inflammatory and sclerotic changes in the components of the respiratory portion occurred, which were manifested by a significant increase in the average values of dys- and atelectasis and the relative areas of emphysematously changed lung tissue relative to the indicators of the intact group. The values of the relative fractions of unchanged lung tissue were significantly reduced, which indicated deep degenerative-destructive changes in the organ.

Keywords: lungs, thermal injury, burn, morphometry.

Introduction

According to the literature, stress can be a pathogenetic link in the development of changes in the structure and function of the cardiovascular system, digestive tract, psychoneurological disorders, immunodeficiency states of the body, and oncological pathology. The pathology of the respiratory system attracts the attention of researchers due to the high level of lung diseases [4, 6].

Thermal burns are one of the most traumatic and physically exhausting injuries [11]. Among the many factors that are decisive in the case of a burn injury, the relationship

between the temperature of the damaging agent and the duration of exposure, known as the time-temperature relationship, which determines the depth of the lesion, is important. The primary reaction of the body to thermal injury is stress. During burns, hypoxic, hemodynamic and metabolic disorders occur, which lead to changes in the structures and functions of internal organs, against the background of significant exo- and endogenous toxemia [3, 10, 17, 20].

There are various ways of developing disorders of the

respiratory system after a burn injury to the skin: direct thermal damage to the respiratory tract, damage to the lungs by toxins of endogenous origin. After thermal exposure, there is a reorganization of the airiness of the lung tissue, its increase and combination with the phenomena of bronchospasm [8]. A complex of morphological changes develops in the lungs, which includes degenerative changes in the walls of blood vessels and their permeability, a violation of the typical structure of the alveoli, as well as the appearance of foci of dys-, atelectasis and atelectasis, signs of inflammatory reactions, and fields of accumulation of alveolar macrophages in the areas of hemorrhages were revealed [21]. Endotheliocytes and alveolocytes were increased in size due to protrusion. Hypertrophy of organelles and fragmentary disruption of membranes were observed. Expressed signs indicated a violation of gas exchange and the development of hypoxia [23].

The aim of the study - to establish changes in the morphometric parameters of the lungs after experimental thermal injury to the skin.

Materials and methods

Simulation of thermal injury was carried out on mature male rats with a body weight of 180-250 g. The animals were kept in standard conditions of the vivarium of the Ivan Horbachevsky Ternopil National Medical University. Animal care and all manipulations were carried out in accordance with the recommendations of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1986), as well as in accordance with the provisions of the "General Ethical Principles for Animal Experiments" adopted by the First National Congress of Bioethics (Kyiv, 2013). *The study was approved by the Bioethics Commission of Ternopil National Medical University, protocol No 59, 05.06.2020.* A skin burn of the IIB degree was applied under thiopental-sodium anesthesia with copper plates heated in boiled water to a temperature of 97-100°C on the depilated surface of the skin of the animal's back, exposition 10-15 seconds. After decapitation, lungs were collected for morphological examination on days 1st, 7th, 14th and 21st of the experiment. After fixation of pieces of tissue in 10 % neutral formalin solution, dehydration in alcohols of increasing concentration and embedding in paraffin, histological sections with a thickness of 5-6 µm were made, which were stained with hematoxylin-eosin [5].

Morphometric studies were carried out using the system of visual analysis of histological preparations. Images from histological preparations were displayed on a computer monitor from a microscope "MICROmed SEO SCAN" and with the help of a video camera "Vision CCD Camera" and the program SEO ImageLAB Bio, and Microsoft Excel, "STATISTICA 12.0" on a personal computer. The parameters were measured at the specified times of the experiment in

slides stained with hematoxylin and eosin. The ratio of the structural components of the lungs was determined: the relative proportion of bronchi, lymphoid tissue and the respiratory portion; in which the relative proportion of lung tissue with unchanged histostructure, atelectasis, dysatelectasis, and emphysematously changed lung tissue were measured.

Results

Morphometric studies of the lung components of the intact animals established that the average value of the relative area of the bronchi was 5.125 ± 0.151 %, the average value of the share of vessels was 4.316 ± 0.132 %, and the average value of the share of the respiratory portion was 84.52 ± 1.30 %. In the connective tissue, bronchovascular stroma, and within the wall of the bronchi and vessels, there was an accumulation of lymphoid tissue, mainly in the form of follicles, which in some places was infiltrated the wall on its entire thickness - from the mucosal tunic to the adventitia. The average value of the relative area of the lymphoid tissue was 6.051 ± 0.235 % (Fig. 1).

The conducted morphometric studies of the components of the respiratory department of the lungs showed that the average value of the relative area of the lung tissue with an unchanged histostructure was 83.31 ± 2.70 %. The average value of the area of atelectasis was 2.741 ± 0.113 %, the relative share of dys-, atelectasis was 4.056 ± 0.170 %, and the relative share of emphysematously changed lung tissue was 9.904 ± 0.215 % (Fig. 2, 3).

One day after the experimental thermal injury, a significant increase in the average value of the proportion of blood vessels was established to 4.808 ± 0.126 % ($p < 0.01$), which was 1.11 times greater than that of animals in the intact group. The relative shares of bronchi and lymphoid tissue also increased significantly, respectively 5.871 ± 0.162 % and 7.485 ± 0.192 % (in both cases $p < 0.001$) compared to intact indicators. However, the average value of the area of the respiratory portion decreased and it was

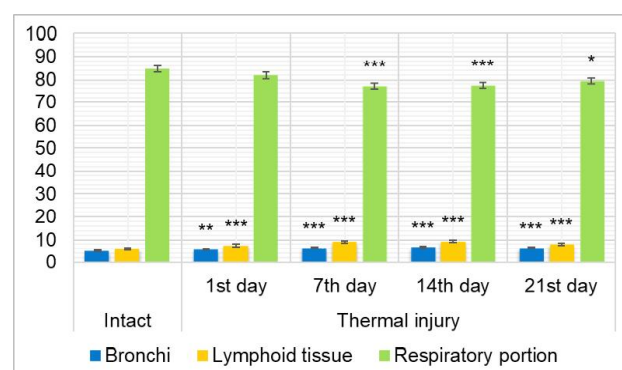


Fig. 1. Ratio of the lungs structural components of the intact group animals and animals at different periods of observation after experimental thermal injury. Notes: * - values that are statistically significantly different from the indicators of animals of the intact group (* - $p < 0.05$; ** - $p < 0.01$; *** - $p < 0.001$).

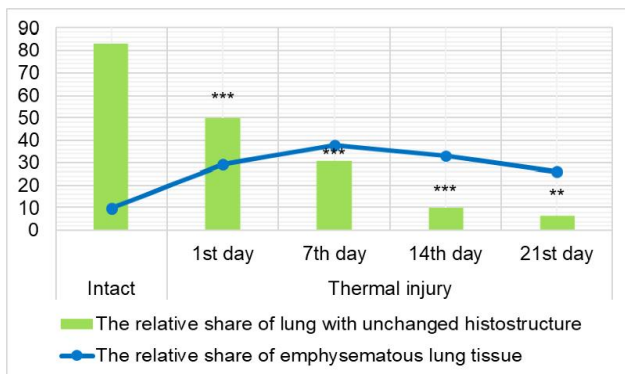


Fig. 2. Ratio of structural components of the respiratory portion of the lungs at different times after experimental thermal injury. Notes: * - values that are statistically significantly different from the indicators of animals of the intact group (** - $p < 0.01$; *** - $p < 0.001$).

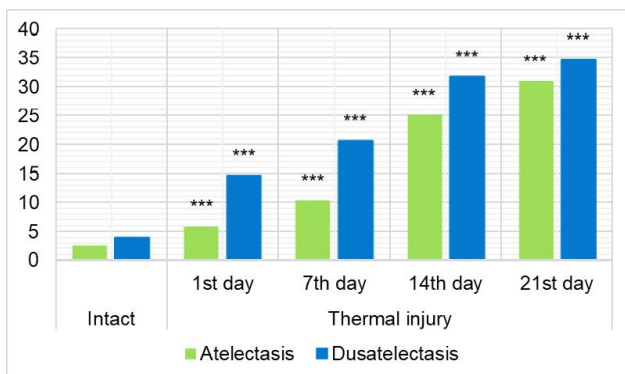


Fig. 3. Dynamics of changes in the structural components of the respiratory portion of the lungs at different times after experimental thermal injury. Notes: * - values that are statistically significantly different from the indicators of animals of the intact group (** - $p < 0.01$; *** - $p < 0.001$).

81.85±1.61 %, which is 0.96 of the normal value. Inter-alveolar septa were thickened both due to edema and blood filling of hemocapillaries and due to leukocyte infiltration. Dis- and atelectasis were found diffusely in the lung parenchyma, near the terminal bronchioles, in which the lumens of the alveoli had a slit-like shape, or they were absent at all. Morphometrically, it was established that their relative shares were significantly increasing and amount to 14.70±0.51 % and 5.941±0.175 % ($p < 0.001$), which were 2.17 and 3.63 times more than indicators of intact group of animals (see Fig. 3). Along with this, undamaged areas of lung tissue were observed, the average value of their area was equal to 50.19±1.30 % ($p < 0.001$), which is reliably 1.66 times less than the indicator of animals of the intact group.

Also, mainly subpleural, significantly refined, emphysematously enlarged alveoli were found. Their relative share reliably increased by 2.95 times compared to the indicator of the intact group of animals and it was 29.17±0.74 % ($p < 0.001$).

After 7 days of the experiment, the relative shares of bronchi and bronchial-associated lymphoid tissue

increased significantly by 28 % and 49 %, respectively, relative to the indicators of animals of the intact group and were equal to 6.546±0.268 % and 9.046±0.301 % (in both cases $p < 0.001$). Morphometric studies of the respiratory portion of the lungs during this period showed that the value of the relative share of lung tissue with unchanged histoarchitectonics decreased by 2.68 times from the intact indicator and amounts to 31.07±1.05 % ($p < 0.001$) (see Fig. 2). However, the relative areas of atelectasis, dis-, atelectases, and emphysema zones increased significantly by 3.80; 5.12 and 3.82 times compared to the values of animals of the intact group and were, respectively, 10.41±0.28 %; 20.72±0.61 % and 37.80±1.07 % (in all cases $p < 0.001$) (see Fig. 3).

Morphometric studies 14 days after experimental thermal injury established a significant decrease in the average value of the relative area of vessels, however, it exceeded the indicator of the intact group of animals by 51 % and was equal to 6.523±0.245 % ($p < 0.001$). The relative shares of bronchi and lymphoid tissue in this period of the experiment were of the greatest importance and reliably exceeded the values of the intact group of animals by 1.31 and 1.54 times, they were 6.704±0.231 % and 9.317±0.356 % (in both cases $p < 0.001$). The average indicator of the respiratory portion of the lungs was equal to 77.47±1.40 % ($p < 0.001$), which was significantly less than the indicator of animals of the intact group. In the respiratory portion of the lungs, it was established that the relative shares of dys- and atelectasis and emphysematously changed areas reliably increase by 7.84; 9.17 and 3.34 times relative to the indicators of the intact group of animals and were 31.76±0.97 %; 25.13±0.74 % and 33.04±0.80 % (in all cases $p < 0.001$) (see Fig. 3). At the same time, the average value of the relative area of the unchanged histostructure of the lung tissue decreases and it was 10.07±0.31 % ($p < 0.001$), which is 8.27 times less than the intact indicator.

After 21 days of the experiment, an increase in the foci of atelectasis and dys-, atelectasis with their infiltration by lymphocytes and sprouting of collagen fibers was noted. The average values of their areas were the highest in this period of observation and they were 31.04±0.95 % and 35.70±0.84 % ($p < 0.001$), which is 11.34 and 8.81 times more than intact indicators (see Fig. 3). Subpleurally, the size of areas of emphysematously dilated alveoli increased with damage to their walls and the release of blood formed elements into their lumen, and their relative share was 26.21±0.69 % ($p < 0.001$), which is 2.65 times higher than the indicator of intact alveoli groups of animals. The smallest average value of the relative area occupied by unchanged lung tissue and it was 7.058±0.245 % ($p < 0.001$), which is 11.82 times less than the intact indicator (see Fig. 2).

Discussion

The results of morphometric studies of the structural components of the lungs in experimental thermal injury

are to a certain extent consistent with the available data of literary sources [1, 7, 12]. In the works of the authors [2, 22], it was established that under the influence of factors of stressogenic origin, changes of a dystrophic nature were observed, namely, the cross-sectional area of the alveoli decreased, and the thickness of the interalveolar partitions increased. We found that 7 days after thermal damage of the skin, the relative proportions of bronchi and bronchial-associated lymphoid tissue in the lung tissue increased significantly, therefore, the average value of the area of the respiratory portion progressively decreased.

Scientists [8, 14, 19] note that with exogenous action, there is a violation of the vessels in the organ, which is accompanied by bronchospasm or acute expansion of the bronchi lumen and leads to damage of the integrity of the lung tissue structural organization. Damage to the respiratory portion of the lungs is confirmed by a significant increase in the average values of dys- and atelectasis and zones of emphysematous expansion of the alveoli, which to some extent agrees with the data of scientists [9, 16]. Morphometric studies [15, 18] noted a significant increase in the rate of fibrosis and hyperplasia of lymphoid tissue under conditions of chronic chemical exposure, which to some extent agrees with our studies. Experimental studies [13] indicated the development of degenerative, inflammatory and sclerotic changes in the components of the respiratory portion.

According to our obtained experimental data, in the late

stages after thermal injury, there was a tendency to increase the average values of dys- and atelectasis and the relative areas of emphysematously changed lung tissue, while the values of the relative fractions of unchanged lung tissue decreased.

Conclusions

1. The results of the morphometric analysis showed that in the early stages (1, 7 days) after experimental thermal injury to the skin, there was a reorganization of the structural components of the lungs with signs of an adaptive and compensatory nature, as well as destructive changes.

2. It was established that the average values of the area of bronchi, lymphoid tissue statistically significantly increased compared to the indicators of intact group animals, while the percentage of unchanged lung tissue significantly decreased in the respiratory portion.

3. It was found that in the late stages of the experiment (14, 21 days), inflammatory and sclerotic changes in the components of the respiratory department occurred, which were manifested by a significant increase in the average values of dys- and atelectasis and the relative areas of emphysematously changed lung tissue relative to the indicators of the intact group. The values of the relative fractions of unchanged lung tissue were significantly reduced, which indicated deep degenerative-destructive changes in the organ.

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МОРФОМЕТРИЧНИЙ АНАЛІЗ ПАРАМЕТРІВ ЛЕГЕНЬ ЗА УМОВ ЗМОДЕЛЬОВАНОЇ ОПІКОВОЇ ТРАВМИ

Лихацький П. Г., Огінська Н. В., Гетманюк І. Б., Небесна З. М., Трач Росоловська С. В.

Термічні опіки є одними з найбільш травматичних та фізично виснажливих ушкоджень. Серед багатьох факторів, які є визначальними при опіковій травмі, важливим є взаємозв'язок між температурою пошкоджуючого агента та тривалістю впливу. Термін впливу та висока температура визначають глибину ураження. При опіках виникають гіпоксичні, гемодинамічні і метаболічні порушення, що призводять до змін структур і функцій внутрішніх органів. Відомі різні шляхи розвитку порушень дихальної системи після опікової травми шкіри: безпосереднє термічне ураження дихальних шляхів, пошкодження легень токсинами ендогенного походження. Після термічного впливу відбувається реорганізація повітряності легеневої тканини, її підвищення та поєднання з явищами бронхоспазму. Розвивається комплекс морфологічних змін у легенях, котрий включає дегенеративні зміни стінок судин та їх проникності, порушення типової будови альвеол, появу осередків дистелектазів і ателектазів, ознаки запальних реакцій, а також виявлення ділянок-скупчень альвеолярних макрофагів у місцях крововиливів. Метою нашого дослідження було встановити зміни морфометричних параметрів легень при експериментальній термічній травмі шкіри. Результати морфометричного аналізу показали, що у ранні терміни (1, 7 доба) після експериментальної термічної травми шкіри відбувається реорганізація структурних компонентів легень з ознаками пристосувального і компенсаторного характеру, а також деструктивними змінами. Встановлено, що середні значення площі бронхів, лімфоїдної тканини статистично достовірно збільшуються порівняно з аналогічними показниками тварин інтактної групи, тоді як у респіраторному відділі достовірно зменшується відсоток незміненої легеневої тканини. Таким чином, виявлено, що у віддалені терміни дослідження (14, 21 доба) відбуваються запальні та склеротичні зміни компонентів респіраторного відділу, котрі проявляються достовірним збільшенням середніх значень дис- та ателектазів, а також відносних площ емфізематозно зміненої легеневої тканини відносно показників інтактної групи. Значення відносних часток незміненої легеневої тканини достовірно знижуються, що вказує на глибокі дегенеративно-деструктивні зміни в органі.

Ключові слова: легені, термічна травма, опік, морфометрія.



Morphometric assessment of the effects of monosodium glutamate on the carotid sinus wall: an experimental study

Sodomora O. O.

Danylo Halitskiy Lviv National Medical University, Lviv, Ukraine

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CORRESPONDING AUTHOR

e-mail: o.sodomora@gmail.com
Sodomora O. O.

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The increase in global burden of stroke is hard to overestimate. Every year it continues to be a leading cause of mortality worldwide. Extracranial pathology of the carotid arteries is a major underlying reason of stroke. Given the role of alimentary factors in the development of atherosclerosis of the carotid arteries, possible influence of food additives on the carotid sinus structure is of special interest. Monosodium glutamate is one of the most common food additives that is allowed for consumption in many countries due to it being considered relatively safe. Recent scientific research however points towards the possible adverse effects of monosodium glutamate on the living organism. The aim of this study was to analyze qualitative and quantitative parameters of carotid sinus structural organization of white male albino rats under normal conditions, in the setting of oral monosodium glutamate consumption and after its withdrawal. Carotid sinuses of 30 white male albino rats that had been daily consuming 10 mg/kg of monosodium glutamate for 4 or 8 weeks with subsequent withdrawal for 2 weeks were subjected to qualitative and quantitative analysis at different time-points of the experiment. The data obtained was compared with the results of morphologic and morphometric study of carotid sinuses of 9 rats of the control group. For morphometric analysis, the following parameters were considered: intima thickness, media thickness, adventitia thickness, diameters of the arterioles, venules and capillaries of the carotid sinus vasa vasorum. Summarizing the morphometric analysis results, it is worth noting that, for the duration of 8 weeks of the experiment, steady increase in the thickness of all layers of the vascular wall, but especially intima and adventitia, was observed in the study group. At the same time, the diameter of the arterioles located in the carotid sinus adventitia was decreasing, while venules and capillaries demonstrated invariable increase of their lumen diameter. After 2 weeks of monosodium glutamate withdrawal, the thickness of intima and adventitia continued to increase, while media thickness had somewhat decreased, probably due to fibrosis and dystrophy. The tendency towards narrowing of the arterioles' lumen and widening of the venules and capillaries persisted for at least 2 weeks despite discontinuation of monosodium glutamate. Therefore, systematic consumption of monosodium glutamate may lead to impairment of carotid sinus structural organization, particularly endothelial proliferation, fibrotic and dystrophic changes of media, adventitia thickening as well as microcirculatory vessels damage, that continue to persist despite the food additive withdrawal.

Keywords: monosodium glutamate, carotid sinus, internal carotid artery, intima, media, adventitia.

Introduction

Cardiovascular diseases, due to their prevalence, as well as a prominent place in the structure of mortality, are a significant medical and social problem [1, 9]. Cerebral stroke ranks 5th among the causes of death and is the leading cause of disability [26]. The pathogenetic basis for the occurrence of morphological changes in tissues and

organs is often micro- and macroangiopathy, which cause tissue trophic disorders and, as a result, their structural rearrangement [12]. Approximately 85 % of all strokes are ischemic strokes, about 20 % of which are caused by extracranial pathology of the internal carotid arteries [21]. Atherosclerotic plaque often occurs in the area of bifurcation

of the carotid arteries, especially in the area of the carotid sinus - a small expansion of the internal carotid artery, which is most often located just cranial to their bifurcation and is an important structure involved in the regulation of hemodynamics. Morphological changes in the area of the carotid sinus can accelerate the formation of atherosclerotic plaque, which, in turn, most often leads to strokes in patients without other known cardiovascular risks [10].

Among all the factors that influence the development of carotid artery pathology, food plays a prominent role, and both the quantitative and qualitative composition of food are of significant importance. In this context, monosodium glutamate is of particular interest - a common food additive that is approved for use in many countries, is considered relatively safe and is widely used to improve the organoleptic properties of food for both adults and children. According to the data of the European Food Safety Authority (EFSA), the acceptable group daily dose of monosodium glutamate was set at the level of 30 mg/kg in terms of glutamic acid, however, in most population groups, the daily consumption of monosodium glutamate not only significantly exceeds this level, but in some of them are even higher than the doses that cause unwanted effects in humans [11]. At this time, the European Commission plans to revise the maximum daily doses of monosodium glutamate allowed for consumption.

Despite the important role of monosodium glutamate in the development of certain pathological conditions, its influence on the structure and function of the vascular bed, in particular the carotid arteries and the carotid sinus, has not been sufficiently studied. However, the role of monosodium glutamate in the development of obesity and hypertension [25], Alzheimer's disease [13], abnormalities in the development of the nervous system [1] and gastric erosions [8] is described in the scientific literature. The relationship between monosodium glutamate consumption and manifestations of toxic effects in tissues of lymph nodes [15], colon [16], liver [6] and reproductive system [20] was also shown. The ability of monosodium glutamate to cause oxidative stress in myocardial cells was also reported, which was characterized by an increase in the levels of marker enzymes [7]. It is also known that monosodium glutamate is capable of inducing obesity and an increase in cholesterol levels, which can lead to an increased risk of cardiovascular events [4]. In view of this, the study of the ways of influence of monosodium glutamate on the morphology of the vascular wall, in particular the wall of the carotid sinus, is important for establishing the mechanisms of its action, the nature of structural changes, as well as identifying possible modifying factors that weaken or modulate this influence.

The purpose of the study: to analyze the qualitative and quantitative parameters of the structural organization of the carotid sinus of white male laboratory rats in normal conditions, under the influence of monosodium glutamate in the experiment, as well as when it is withdrawn.

Materials and methods

39 male white laboratory rats aged 3.5-5.0 months with an initial body weight of 180-200 g were involved in the study, which were equally divided into experimental groups (subgroup 1, n=10; subgroup 2, n=10; subgroup 3, n= 10) and control (n=9) groups. Experimental group animals received 10 mg/kg/day orally administered monosodium glutamate for 4 (subgroup 1) or 8 weeks (subgroup 2), while control group animals received no dietary supplements. After 8 weeks of the experiment, monosodium glutamate administration was discontinued, instead, the experimental animals were transferred to a standard vivarium diet with an assessment of the morphological structure of the wall of their carotid sinus 2 weeks after withdrawal (subgroup 3).

The animals were kept in cages of 4 individuals each, in a well-ventilated and lighted room of the vivarium, and had unlimited access to food that corresponded to the standard diet of the vivarium. Throughout the experiment, the principles of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986), the norms of the Law of Ukraine No. 3447-IV "On the Protection of Animals from Cruelty Treatment", general ethical principles of experiments on animals, adopted by the First National Congress of Ukraine on Bioethics (2001), which was confirmed by the commission on the ethics of scientific research, experimental developments and scientific works of Danylo Halitskiy Lviv National Medical University (protocol No. 3 dated 11.3.2022).

4 weeks after the beginning of the study, 10 animals of the research group (subgroup 1) were removed from the experiment by overdose of ether anesthesia; another 10 animals of the experimental group were removed from the experiment at the end of 8 (subgroup 2) and 10 (subgroup 3) weeks, respectively. The research material is represented by histological preparations of the carotid sinus of white rats, made by making sections of the tissue of the bifurcation of the carotid arteries from previously prepared paraffin blocks. For histological examination, the sections were stained with methylene blue and hematoxylin-eosin. The preparations were studied and photographed at magnifications of the microscope: x200, x400, x1000. The "Aver Media" computer system was used to photograph micropreparations. The ImageJ program was used for morphometric analysis. In order to evaluate the morphometric indicators, the following parameters were analyzed: the thickness of the intima of the carotid sinus wall, the thickness of the media of the carotid sinus wall, the thickness of the adventitia of the carotid sinus wall, the diameter of the vessels of the microcirculatory bed (vasa vasorum) located in the adventitia of the carotid sinus.

Statistical data processing was performed using MS Excel 2007 software. Experimental data are presented as the average value of the sample parameter and its standard deviation ($M \pm \sigma$). Since the general variances of the studied values are unknown, the sample means are subject to the Student's t-distribution.

Results

During the morphological study of the studied area of the carotid sinus of a white rat, it was found that the internal and external carotid arteries originated from the common carotid artery, the bifurcation of the common carotid artery was located behind the posterior angle (large horn) of the hyoid bone, 2-4 mm below the latter in both animals groups. The diameter of the internal carotid artery practically corresponded to that of the external carotid artery. During histological examination (staining with methylene blue and hematoxylin-eosin), the wall of both carotid arteries consisted of clearly defined three layers: inner - intima, middle - media, and outer - adventitia, in which small blood vessels, known as vasa vasorum, were visible.

The structural organization of the carotid sinus wall in animals of the control group was characterized by the following parameters: intimal thickness $4.362 \pm 0.494 \mu\text{m}$, media thickness $47.17 \pm 0.99 \mu\text{m}$, adventitia thickness $75.36 \pm 0.68 \mu\text{m}$. As for vasa vasorum, the diameter of arterioles in the control group was $20.73 \pm 0.71 \mu\text{m}$, venules $32.27 \pm 0.63 \mu\text{m}$, capillaries $6.249 \pm 0.391 \mu\text{m}$.

At the end of the 4 week of monosodium glutamate use, moderate swelling of the carotid sinus wall in the area directly above the bifurcation was observed in the experimental animals of subgroup 1 when compared with the control group, as well as fibrosis and hyperemia of the adventitia capillaries. The wall of individual capillaries was damaged, isolated diapedesis hemorrhages were also detected (Fig. 1). The pronounced multiplication and folding of the intima attracted attention (Fig. 2). Morphological changes at the end of the 4th week of the experiment were characterized by the following morphometric parameters: intima thickness $6.873 \pm 0.668 \mu\text{m}$ (control $4.322 \pm 0.524 \mu\text{m}$, $p < 0.05$), media thickness $60.68 \pm 0.91 \mu\text{m}$ (control $46.81 \pm 1.12 \mu\text{m}$, $p < 0.05$), adventitia thickness $81.13 \pm 1.93 \mu\text{m}$ (control $75.22 \pm 0.71 \mu\text{m}$, $p < 0.05$). Regarding the vasa vasorum, the diameter of the arteriole in the experimental group was $16.67 \pm 0.51 \mu\text{m}$ (control $21.21 \pm 0.67 \mu\text{m}$, $p < 0.05$), venules $42.22 \pm 0.78 \mu\text{m}$ (control $32.714 \pm 0.576 \mu\text{m}$, $p < 0.05$), capillary $8.247 \pm 0.231 \mu\text{m}$ (control $6.224 \pm 0.324 \mu\text{m}$, $p < 0.05$).

After 8 weeks of consumption of monosodium glutamate by experimental animals of subgroup 2, the wall of their carotid sinus was disorganized, the intimal layer of endotheliocytes was deformed, often without clear contours, in some places interrupted, protrusions of the endothelium, proliferation of endotheliocytes, and in some places - exfoliation of endotheliocytes into the lumen of the carotid sinus were observed (Fig. 3). Bundles of smooth myocytes of the muscle media were separated by wide layers - thickened elastic membranes, often deformed. Perivascular edema, dilatation of vasa vasorum, thickening of arteriole walls were observed, formation of wall thrombi occurred in lumens (Fig. 4). At the end of the 8th week of the experiment, the morphometric parameters were: intima thickness $9.552 \pm 0.724 \mu\text{m}$ (control $4.337 \pm 0.564 \mu\text{m}$, $p < 0.05$), media thickness $81.52 \pm 2.31 \mu\text{m}$ (control $46.92 \pm 0.98 \mu\text{m}$, $p < 0.05$), adventitia thickness $126.1 \pm 0.7 \mu\text{m}$ (control $74.98 \pm 0.64 \mu\text{m}$,

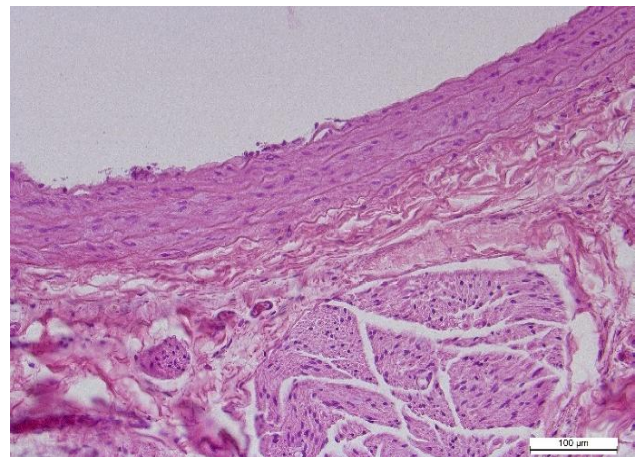


Fig. 1. A fragment of the carotid sinus wall of a white rat after 4 weeks of monosodium glutamate consumption. Hematoxylin-eosin staining. x200.

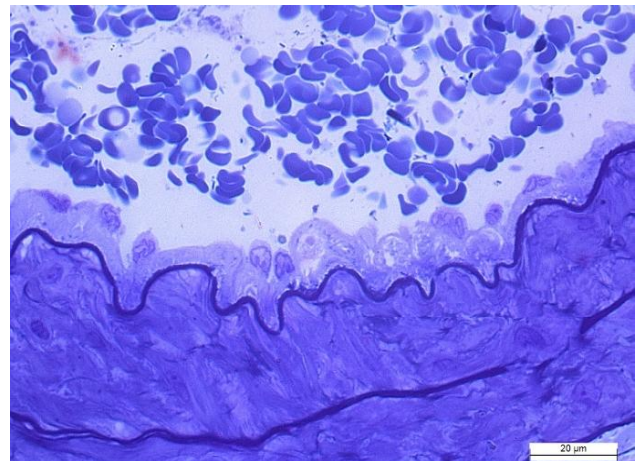


Fig. 2. A fragment of the carotid sinus wall of a white rat after 4 weeks of monosodium glutamate consumption. Staining with methylene blue. x1000.

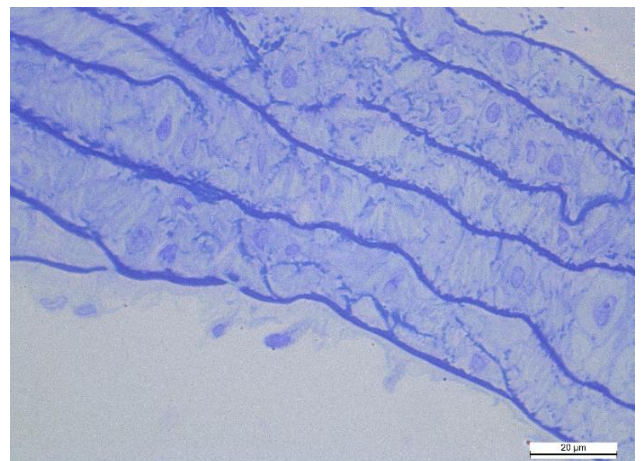


Fig. 3. A fragment of the wall of the carotid sinus of a white rat after 8 weeks of monosodium glutamate consumption. Staining with methylene blue. x1000.

$p < 0.05$). Regarding the vasa vasorum, the diameter of the arteriole in the experimental group was $13.04 \pm 0.45 \mu\text{m}$

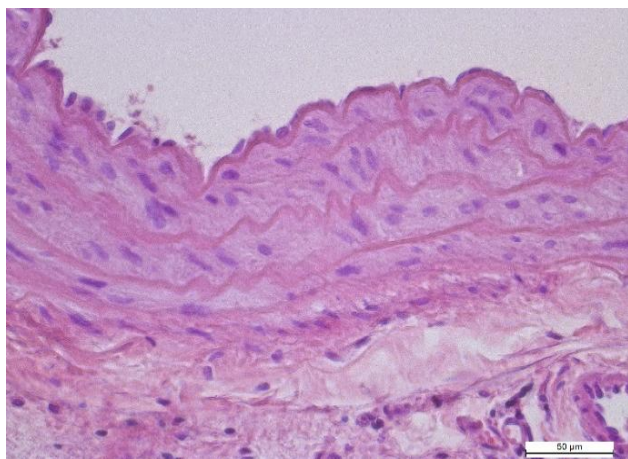


Fig. 4. A fragment of the wall of the carotid sinus of a white rat after 8 weeks of monosodium glutamate consumption. Hematoxylin-eosin staining. x400.

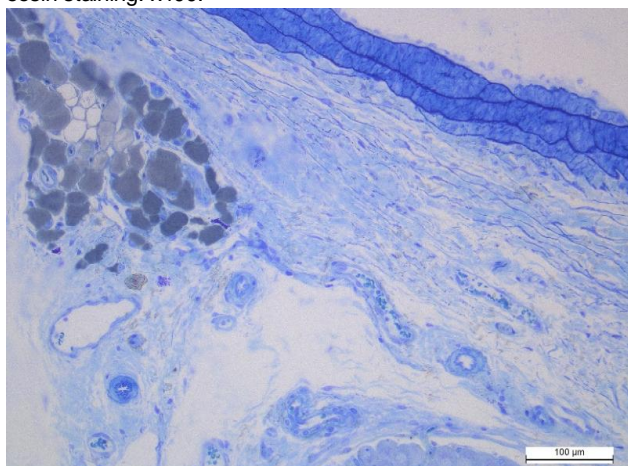


Fig. 5. A fragment of the carotid sinus wall of a white rat after 8 weeks of monosodium glutamate consumption and 2 weeks of its withdrawal. Staining with methylene blue. x200.

(control $20.86 \pm 0.74 \mu\text{m}$, $p < 0.05$), venules $63.26 \pm 1.50 \mu\text{m}$ (control $32.68 \pm 0.62 \mu\text{m}$, $p < 0.05$), capillary $9.044 \pm 0.338 \mu\text{m}$ (control $6.142 \pm 0.443 \mu\text{m}$, $p < 0.05$).

At the end of the 10 week of the experiment, that is, at the end of 2 weeks from the moment of discontinuation of monosodium glutamate, compensatory processes in the wall of the carotid sinus were practically not observed in animals of subgroup 3, which previously received it orally for 8 weeks. Thickening of the wall of the carotid sinus due to adventitia and, to a lesser extent, intima was noted, signs of exudative-proliferative inflammatory process prevailed, vacuolar dystrophy of myocytes and fibro-sclerotic changes, deformation of elastic membranes, which led to a relative decrease in its thickness, were observed in the media. In the significantly thickened adventitia, with interspersed fat, structural changes were detected on the part of all vessels of the vasa vasorum: hyperemia of capillaries, reduction of the lumen of arterioles due to thickening and swelling of their walls, formation of paramural thrombi, expansion and thinning of venule walls, perivascular edema (Fig. 5). The

morphometric parameters of subgroup 3 were: intimal thickness $14.71 \pm 0.88 \mu\text{m}$ (control $4.352 \pm 0.478 \mu\text{m}$, $p < 0.05$), media thickness $57.33 \pm 1.34 \mu\text{m}$ (control $46.63 \pm 0.96 \mu\text{m}$, $p < 0.05$), adventitia thickness $236.6 \pm 1.3 \mu\text{m}$ (control $75.43 \pm 0.76 \mu\text{m}$, $p < 0.05$). Regarding the vasa vasorum, the diameter of the arteriole in the experimental group was $11.12 \pm 0.89 \mu\text{m}$ (control $20.47 \pm 0.58 \mu\text{m}$, $p < 0.05$), venules $102.1 \pm 1.3 \mu\text{m}$ (control $32.35 \pm 0.62 \mu\text{m}$, $p < 0.05$), capillary $10.03 \pm 0.56 \mu\text{m}$ (control $6.319 \pm 0.442 \mu\text{m}$, $p < 0.05$).

The dynamics of changes in the thickness of the layers of the carotid sinus wall are shown in the graphs (Figs. 6, 7 and 8).

The dynamics of changes in blood vessels of the hemomicrocirculatory bed (vasa vasorum) are shown in the graphs (Figs. 9, 10 and 11).

Summarizing the results of the morphometric study, it should be noted that during the 8 weeks of the experiment in the experimental group, the thickness of all layers of the vascular wall, especially the intima and adventitia, decreased, the diameter of arterioles decreased, and the diameter of venules and capillaries of the hemomicrocirculatory channel increased. After withdrawal of sodium glutamate, the thickness of the adventitia and intima continued to increase, but the thickness of the media decreased slightly, presumably

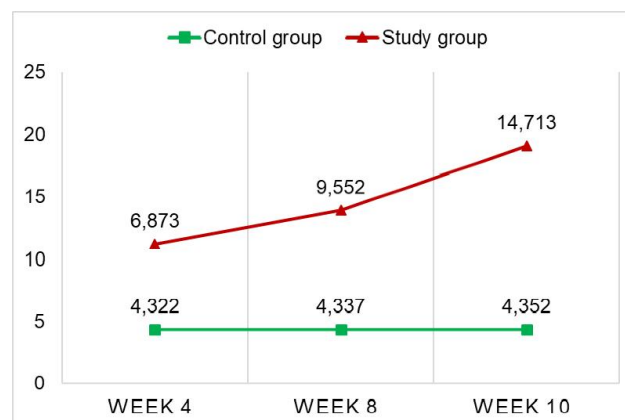


Fig. 6. The thickness of the carotid sinus intima wall of a white laboratory rat (μm).

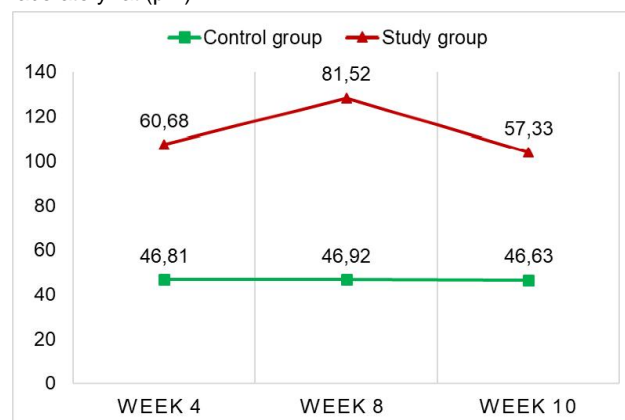


Fig. 7. The thickness of the carotid sinus media wall of a white laboratory rat (μm).

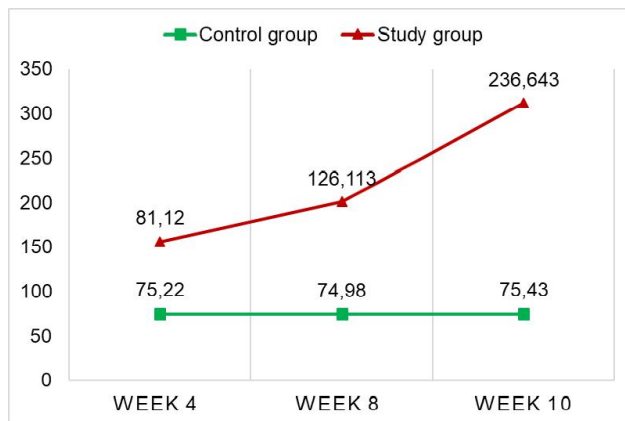


Fig. 8. The thickness of the carotid sinus adventitia wall of a white laboratory rat (µm).

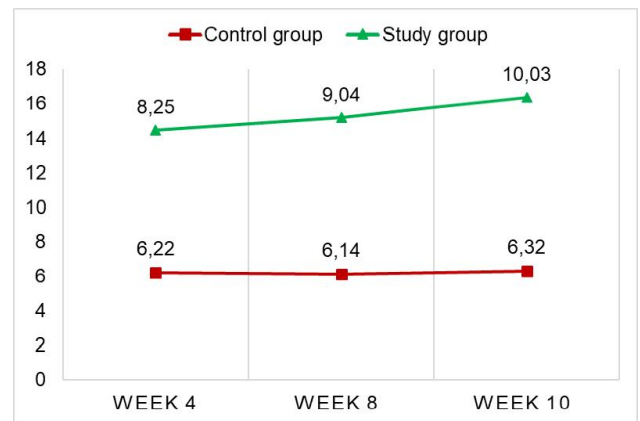


Fig. 11. The diameter of the carotid sinus capillaries wall of a white laboratory rat (µm).

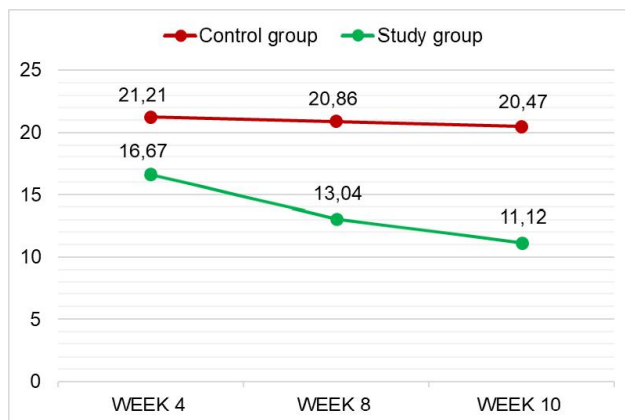


Fig. 9. The diameter of the carotid sinus arterioles wall of a white laboratory rat (µm).

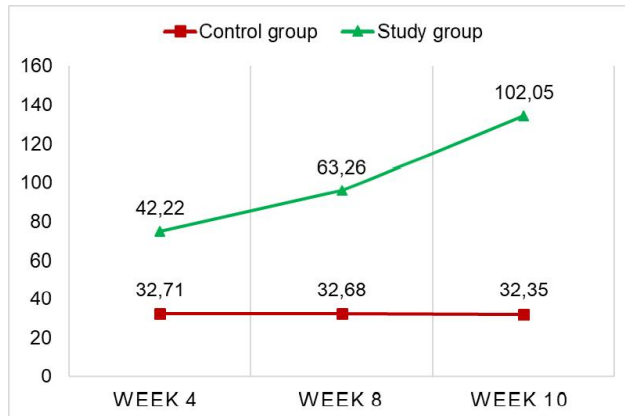


Fig. 10. The diameter of the carotid sinus venules wall of a white laboratory rat (µm).

due to fibro-dystrophic changes. The tendency to narrowing of the lumen of arterioles and expansion of the lumen of venules and capillaries persisted 2 weeks after withdrawal of monosodium glutamate.

Discussion

Extracranial pathology of the carotid arteries is an important risk factor for the development of brain perfusion

disorders, which can be manifested by a wide range of pathological conditions, from cognitive disorders to cerebral stroke [18]. In this context, the attention of the scientific community has been focused on the study of the mechanisms of influence of the most common food additive - monosodium glutamate, on the living organism for several decades. Scientific studies have proven that its long-term use is associated with the development of a number of pathological conditions, including metabolic syndrome, diabetes, dyslipidemia and obesity, hypertension and other diseases of the cardiovascular system, neuroendocrine disorders, depression and anxiety [17, 19], disorders of the urinary and reproductive systems [23], liver diseases [5].

The results of our research indicate that the adverse effect of monosodium glutamate on the structural organization of the carotid sinus is noticeable after four weeks of its consumption and increases in dynamics. These effects do not diminish with withdrawal of glutamate. Thus, after 4 and 8 weeks of the experiment, histological examination reveals significant changes in the structure of the wall of the carotid arteries in the area of the carotid sinus at the microscopic level, which can be directly related to the harmful effect of monosodium glutamate. In particular, the changes we discovered on the part of the endothelium may indicate the ability of monosodium glutamate to cause its proliferation with subsequent violations of the structure of the inner layer of the vascular wall, which may in turn contribute to the development of atherosclerotic plaques and thrombus formation in dynamics.

The mechanisms and role of endothelial dysfunction are actively studied and described in the specialized literature [24, 28], in particular in the context of the ability of monosodium glutamate to provoke endothelial damage [2]. In our study, special attention was paid to the progressive thickening of the carotid sinus wall, especially due to the adventitia, which can potentially play a significant role in the development of atherosclerotic lesions of the carotid artery wall. Our data are confirmed in the professional literature, where it was reported, in particular, about the thickening of the adventitia of the carotid arteries and the thickening of

collagen, which is part of the wall of the carotid artery, in an experiment under the influence of dietary factors, in particular under the conditions of consumption of a high-salt diet [14]. In turn, the consumption of monosodium glutamate in combination with a high-fat diet led to an increase in nitric oxide levels and, as a result, the development of oxidative stress, which, in turn, increased the area of damage during myocardial infarction in the experiment [3].

The structural changes in myocytes of the middle layer of the carotid sinus wall that we discovered were similar to the described damage to cardiomyocytes in ischemia or diabetes [22, 27].

An important pathogenetic factor in the development of damage to the vascular wall is a violation of its microcirculation. The changes in the blood vessels of the hemomicrocirculatory channel that we discovered indicate the probable ability of monosodium glutamate to lead to structural disorders of arterioles, venules and capillaries of the vasa vasorum, and therefore to create conditions for the development of hypoxic-ischemic and stagnant changes in the wall of the carotid sinus. Of particular interest is the fact that the above-described morphological disorders, presumably related to the influence of monosodium

glutamate, increased even two weeks after its withdrawal. This may indicate the ability of monosodium glutamate to trigger a cascade of vascular wall damage processes, which are potentially significant risk factors in the context of the development of cerebrovascular disorders.

Taking into account the possible adverse effect of even low doses of monosodium glutamate on the structural organization of the carotid sinus, which has a tendency to progress and the absence of positive dynamics after the withdrawal of the mentioned food additive, further research is needed to find the possibilities of correcting or leveling this effect, as well as studying the degree of severity and duration pathological effects of applied doses of glutamate.

Conclusion

Monosodium glutamate with systematic oral use can lead to a violation of the structural organization of the wall of the carotid sinus, in particular to the proliferation of the endothelium, fibro-dystrophic changes in the media, thickening of the adventitia, and damage to the vessels of the microcirculatory channel, which continue to increase even after its withdrawal.

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МОРФОМЕТРИЧНА ХАРАКТЕРИСТИКА СТІНКИ СОННОЇ ПАЗУХИ ЗА УМОВ ВПЛИВУ ГЛУТАМАТУ НАТРІЮ В ЕКСПЕРИМЕНТІ Содомира О. О.

Значення мозкового інсульту важко переоцінити: з року в рік він залишається одним із лідерів в структурі смертності. Екстракраніальна патологія сонних артерій, зокрема ділянки сонної пазухи, є однією з провідних причин мозкового інсульту. З огляду на роль аліментарних чинників в розвитку атеросклерозу сонних артерій, особливий інтерес становить вивчення впливу поширених харчових добавок на структурну організацію сонної пазухи. Глутамат натрію - одна із найпоширеніших харчових добавок, яка вважається безпечною і часто застосовується в харчовій промисловості. Однак сучасні наукові дослідження вказують на можливий несприятливий вплив глутамату натрію на структуру і функції органів і тканин живого організму. Метою дослідження було проаналізувати якісні і кількісні параметри структурної організації ділянки сонної пазухи білих лабораторних щурів-самців в нормі, під впливом глутамату натрію в експерименті, а також при його відміні. Досліджено ділянку сонної пазухи і виконано морфометричний аналіз її стінки у 30 лабораторних білих щурів самців, котрі впродовж 4 або 8 тижнів отримували глутамат натрію перорально в дозі 10 мг/кг/добу з подальшою його відміною, що тривала 2 тижні, морфологічним і морфометричним методами на макро- та мікроструктурному рівнях через 4, 8 і 10 тижнів експерименту. Отримані дані порівняні з результатами морфологічного і морфометричного дослідження аналогічної ділянки у 9 тварин контрольної групи. Для оцінки морфометричних показників проаналізовано наступні параметри: товщина інтими стінки сонної пазухи, товщина медії стінки сонної пазухи, товщина адвентиції стінки сонної пазухи, діаметр судин мікроциркуляторного русла (*vasa vasorum*), розташованих в адвентиції сонної пазухи. Підсумовуючи результати морфометричного аналізу, слід зазначити, що протягом 8 тижнів експерименту в дослідній групі збільшувалась товщина всіх шарів судинної стінки, особливо інтими і адвентиції, зменшувався діаметр артерій і збільшувався діаметр венул і капілярів гомомікроциркуляторного русла. Через 2 тижні після відміни глутамату натрію товщина адвентиції та інтими продовжувала зростати, однак товщина медії дещо зменшилася, імовірно за рахунок фіброзно-дистрофічних змін. Тенденція до звуження просвіту артерій і розширення просвіту венул і капілярів зберігалася і через 2 тижні після відміни глутамату. Таким чином, глутамат натрію при систематичному пероральному вживанні може призводити до порушення структурної організації стінки сонної пазухи, зокрема до проліферації ендотелію, фіброзно-дистрофічних змін медії, потовщення адвентиції та пошкодження судин мікроциркуляторного русла, які продовжують наростати навіть після його відміни.

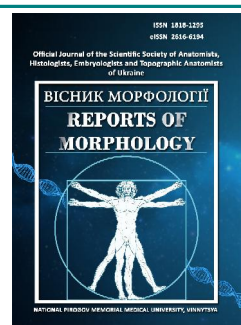
Ключові слова: глутамат натрію, сонна пазуха, внутрішня сонна артерія, інтима, медія, адвентиція.



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Morphological features of heart damages caused by national Uzbek knives

Boymanov F. Kh., Kushbakov A. M.

Samarkand State Medical University, Samarkand, Republic of Uzbekistan

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CORRESPONDING AUTHOR

e-mail: boymanovf@mail.ru

Boymanov F. Kh.

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Damage to the body caused by the action of sharp objects is one of the topical topics of forensic criminology. The variety of existing objects that can potentially be used for the purpose of committing a crime require a detailed traceological study. Purpose of the work: to carry out an analysis according to the study of the features of the morphology of heart stab-cut wounds, inflicted by national Uzbek knives. The material presented by 30 observations of those who died as a result of inflicting penetrating stab wounds with damage to the heart, inflicted by national Uzbek knives. Statistical processing of the obtained results was carried out using the MS Excel 2007 software. It was found that stab-cut wounds were more common in men, the wounds were mainly in the ventricles and less often in the atria. Stab-cut wounds inflicted by Uzbek national knives have an angular, oval, linear shape. The butt ends are П-, Г-, T-shaped, the blade ends are sharp. It was revealed that the walls of the heart, in comparison with skin wounds, have a higher morphological identification significance. The heart after restoration in Ratnevsky's solution deformed less than skin wounds, and the length of the stab-cut wounds of the heart more accurately corresponds to the width of the blade of a stab-cut weapon. This may be due to the peculiarities of the structure of the epicardium and myocardium, which are less susceptible to the process of retraction. On the tissues of the heart, the design features of the butt and blade of knife blades are quite fully determined, so they can be used for group identification of a traumatic weapon.

Keywords: Uzbek national knife, stab-cut wound, skin, heart.

Introduction

Injuries caused by sharp objects include injuries caused by stabbing and cutting weapon [3, 15]. Damage to the heart by stabbing-cutting weapon is more common than other organs, and the lethality from it exceeds 90 % [17].

The prevalence of cases of the use of sharp objects for the purpose of murder or suicide is quite heterogeneous in the world. Thus, an analysis of 30 years of observation data in the city of Brescia (Italy) showed that 131 deaths were committed with the use of such objects, of which 92 were murders, 28 were suicides, and 11 were accidents. In the case of murders, wounds were mostly found in the left part of the front abdominal wall [21].

Monitoring in the city of Melbourne (Australia) from 2001 to 2014 revealed 56 cases of murder. In 45 cases, a cut wound was found in the chest area. Localization on the left side also prevailed [2].

In Bexar County, Texas (USA) from 1988 to 2010, 418 deaths were committed with the use of sharp objects, of which 349 were murders. In most cases, damage to the

heart and lungs was detected. The average number of wounds was 5.3 [8].

An analysis of data from Denmark for the years 1992-2016 showed that in 75 % of murders committed with the use of a sharp object, there was damage to the heart and lungs (in particular, the pericardium and the occurrence of hemo- and pneumothorax, respectively). In 18.9 % of cases, the deceased had one injury in the chest wall. The most common item was a kitchen knife [19].

Thus, the greatest interest in the case of the use of sharp objects causes damage to the heart. An interesting fact is that according to the data of modern research most knife blade characteristics remain unaltered by heat, except for floor angle and slope height of cut. Such is the conclusion of an experimental study conducted by Lukas Waltenberger and Holger Schutkowski [22].

The study of soft tissue objects is a more difficult task for conducting experimental research. Compared to bone objects, which even after exposure to high temperatures

can fully convey all the details of a sharp object that caused damage [20], soft tissue objects, such as the heart, can change their dimensions in the postmortem period and thus deform the picture of the damage.

However, the morphological pattern of the heart and peritoneum damage, as well as damage to the parietal pleura and the specific pattern of a sharp object, have not been studied enough [6, 13]. Although the size, shape, and defects of a sharp object are well reflected in the heart, there are no clear guidelines and recommendations in the literature for assessing pathomorphological changes in the myocardium in stab wounds of the chest with a sharp object [7, 9].

Thus, by combining the actualities given by us, it can be noted that there is a need to determine the features of the morphological and metric signs of stab wounds of this organ, caused by the national Uzbek knives "pichak", from the impact of which non-fatal and fatal injuries occur in various regions of the Republic of Uzbekistan, as national Uzbek knives have their characteristic design features [1].

Purpose of the work: to analyze features of the morphology of heart stab wounds caused by national Uzbek knives.

Materials and methods

The study included materials from 30 people who died as a result of trauma caused by stabbing and cutting tools with damage to the heart, caused by national Uzbek knives. Of these, 21 of the dead were men, and 9 were women, the age of the victims was from 18 to 61 years. In 26 cases, there were single wounds, in 3 cases there were double wounds of the heart, in one case, a heart injury occurred as a result of three impacts with a piercing-cutting tool.

The conducted research does not contradict the basic bioethical norms of the Declaration of Helsinki, the Convention of the Council of Europe on Human Rights and Biomedicine (1977), the relevant provisions of the WHO and the laws of the Republic of Uzbekistan.

All existing lesions were examined in layers on all tissues along the wound channel: on the skin, on all layers of the heart (pericardium, epicardium, myocardium). For additional research, a section of the skin and heart with existing injuries was removed. The study of damage was carried out visually, stereomicroscopically, large-scale photography, measurement and comparison were carried out. A morphological study was performed after the restoration of skin flaps and heart walls with existing lesions in the solution of A. N. Ratnevsky. The study used a ruler with a division value of 0.1 cm, a caliper with a division value of 0.01 cm, an MBS-2 stereomicroscope with side illumination and a magnification of 3.6-12.0 times; digital camera "NikonD5300"; macrophotography was carried out using an MBS-2 microscope. Statistical processing of the obtained results was carried out using MS Excel 2007 software.

Results

In our study, it was found that in 26 (86.6 %) cases, the wounds were often located in the region of the ventricles, in

four (13.4 %) cases, in the region of the atria. Skin wounds were 0-1 cm long in one (3.3 %), 1-5 cm in twenty-eight (93.3 %), 5-8 cm in one (3.3 %), width 0-1 cm in twenty-seven (90.0 %), 1-5 cm - in three (10.0 %) cases, and heart wounds: 0-1 cm in five (16.6 %), 1-5 cm - in twenty-one (70.0 %), 3-5 cm - in four (13.4 %) cases, the width of the wounds in all thirty (100 %) cases were 0-1 cm.

Skin wounds in eleven (36.7 %) cases most often had a sickle-linear shape, in four (13.3 %) - angular, in ten (33.3 %) - arcuate-linear, linear - in five (16.6 %) cases. Heart wounds in eleven (36.7 %) cases had an angular shape, in twelve (40.0 %) - oval, in seven (23.3 %) - crescent-linear. When studying the direction of the wound channel, they were located perpendicularly, vertically, obliquely or at an angle to the surface of the heart. In cases where the channel was located in an oblique direction, the width of the blade was judged by the size of the cross section of the wound channel. During a normal examination, the walls of the wound channel were relatively smooth, and a stereomicroscopic examination revealed small irregularities due to the structure of the muscle tissue.

With a penetrating wound of the heart, the following was noted - the lesions on the skin and cardiac muscle had smooth, well-matched edges. In a stereomicroscopic study, the butt ends were П-shaped in nine (30.0 %) cases, Г-shaped in four (13.3 %), Т-shaped in five (16.6 %), and rounded П-shaped in twelve (40.0 %) cases. The blade ends of the wounds in twenty-eight (93.3 %) cases were sharp, in five (16.7 %) cases additional injuries were noted in the form of parallel linear cuts in two (6.7 %) cases and tears in three (10.0 %) cases. Tears gave the blade end of the wound an Г- or Т-shape; they differed from incisions in uneven edges.

The edges of the wound channel from the action of the blade are sharp, and, according to the action of the butt of the blade, they are Г-, Т-, П-shaped, sometimes rounded. On the walls of the wounds, hemorrhages were noted in twenty-two (73.3 %) cases.

Damage to the heart sac was studied from its inner surface, since the study of the outer surface was not possible due to fat deposits. Damage to the heart sac had a slit-like or fusiform shape. According to the action of the butt of the blade, the ends of the cut were П-shaped or rounded. As you know, the collagen fibers of the pericardium are arranged in two layers. In one of them, the end of the incision was П-shaped, in the other, it was rounded or sharp. In this case, sometimes the tissue fibers of one layer overlap part of the wound opening in another layer. The ribs of the wound channel at the blade ends were sheer or gentle, at the butt ends - sheer or overhanging.

In our study, several features were found in the wall of the heart, which, compared with skin wounds, have a higher morphological identification significance. As a result of morphological studies, the following was revealed that skin wounds after restoration in Ratnevsky solution No. 1 decrease in length and become shorter by 3-13 mm as a

result of elastic fiber contraction. After restoration in Ratnevsky's solution No. 1, the wall of the heart with damage deformed less than skin wounds (2-3 mm), this was due to the thickness and structural features of the myocardium.

The results obtained indicate that the length of stab-cut wounds of the heart, in comparison with skin wounds, more accurately corresponds to the width of the blade of a stab-cutting weapon. This may be due to the peculiarities of the structure of the epicardium and myocardium, which are less susceptible to the process of retraction.

Discussion

Thus, stab wounds were more common in men, the wounds were mainly in the ventricles and less often in the atria. Stab wounds caused by Uzbek national knives have an angular, oval, linear shape. The butt ends are П-, Г-, Т-shaped, the blade ends are sharp.

The data obtained by us confirm the results of studying the morphological features of stab wounds, which allow us to believe that the retraction of lesions on the parietal pleura, heart sac, epicardium and heart muscle is much less than the retraction of skin wounds. As a result, they more accurately reflect the width of the knife blade. In addition, the design features of the butt and blade of knife blades are quite fully determined on the tissues of the heart, so they can be used for group identification of a traumatic tool [6]. When injured using a serrated knife, grooves can be found on the wall of the wounds from the points of notches on the edge of the blade. Evaluation of grooves in soft tissues is a means of identifying a tool that has a serrated blade. To do this, the walls of the stab wounds were exposed, documented by photography and cast using an impression material used in dentistry. The grooves were not identified in the wound marks obtained from knives with a smooth blade [15]. The grooves on the wall of the wounds were visible in experimental wounds in the liver, heart and aorta of animals. When studying stab wounds, it is proposed to open the walls of a stab wound in order to find the striation of the tissue to identify a tool with a serrated blade [14].

In general, the problem of describing injuries caused by sharp objects remains relevant for forensic medicine even today. Even the use of modern instrumental research methods does not allow to avoid such simple mistakes as the use of non-standard damage terminology [11].

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The human body has a heterogeneous resistance to the occurrence of a stab wound. A study conducted on the corpses of 6 people showed that in places where there is cartilage or bone tissue under the skin, such wounds occur with the application of greater force than in areas where there are only soft tissues under the skin. In general, the occurrence of a stab wound in any case requires a force of at least 261 N [4].

In addition to the object that causes the formation of a wound, it is equally important to take into account the circumstances of the injury, which leads to the occurrence of a specific localization and nature of the injury. A vivid example of this is the ritual suicide known as harakiri, when a sharp instrument is used to inflict a wound to the abdomen, causing disembowelment [12]. Ritual suicides with other locations are also described in the world literature and can also be located in the sternocleidomastoid region [10].

Another problem that appears before the forensic medical expert when examining wounds caused by sharp objects is both the variety of old (traditional, folk) tools and the emergence of new, completely unfamiliar types of knives. So, the authors of one of the practice cases dealt with a murder committed by what they called a "Fantasy Knife", which was most likely created on the basis of inspiration from a work or film in the fantasy genre [16].

Even long-known sharp tools can cause misunderstandings when examining the wounds they created. So, it is described that a survival knife, despite being a single-edge blade type of weapon, can cause wounds, the ends of which will be both sharp-angled [5].

The short traditional Japanese wakizashi sword is described as forming a wound channel about 44 cm long and about 9 cm deep with smooth walls [18]. Thus, the study of injuries caused by the use of traditional sharp weapons and various organs that they can affect is still relevant.

Conclusion

The data obtained on the morphological features of stab-cut injuries of the heart indicate that they quite fully reflect the design features of knife blades, which can be taken into account as evidence for identifying a traumatic object. Comparative morphological assessment of skin wounds and heart injuries indicates a higher identification significance of myocardial injuries in stab-cut injuries.

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МОРФОЛОГІЧНІ ОСОБЛИВОСТІ ПОШКОДЖЕНЬ СЕРЦЯ, ЗАПОДІЯНИХ НАЦІОНАЛЬНИМИ УЗБЕЦЬКИМИ НОЖАМИ

Бойманов Ф. Х., Кушбаков А. М.

Ушкодження тіла, спричинені дією гострих предметів, є однією з актуальних тем судово-медичної криміналістики. Різноманіття існуючих предметів, що потенційно можуть бути застосовані з метою вчинення злочину, вимагають детального трасологічного дослідження. Мета роботи: провести аналіз за даними вивчення особливостей морфології колото-різаних ран серця, завданих національними узбецькими ножами. Досліджено матеріал, представлений 30 спостереженнями загиблих внаслідок заподіяння проникних колото-різаних поранень із пошкодженням серця, завданих національними узбецькими ножами. Статистичну обробку отриманих результатів проведено за допомогою програмного забезпечення MS Excel 2007. Встановлено, що колото-різані рани зустрічалися частіше у чоловіків, рани в основному знаходилися в ділянці шлуночків і рідше в ділянці передсердь. Колото-різані рани, нанесені узбецькими національними ножами, зазвичай, кутподібної, овальної або лінійної форми. Обушкові кінці мають П-, Г-, Т-подібну форми, лезові кінці гострі. Виявлено, що стінки серця, порівняно зі шкірними ранами, мають більш високу морфологічну ідентифікаційну значущість. Серце після відновлення в розчині Ратневського деформувалося менше, ніж шкірні рани, і довжина колото-різаних ран серця більш точно відповідає ширині клинка колючо-ріжучої зброї. Це може бути пов'язано з особливостями структури епікарда та міокарда, які менш схильні до процесу ретракції. На тканинах серця досить повно визначаються конструктивні особливості обуху і леза клинків ножів, тому їх можна використовувати для групової ідентифікації зброї, що травмує.

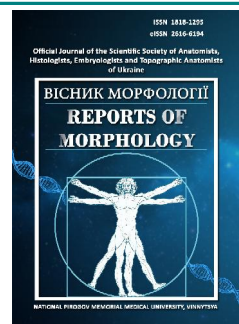
Ключові слова: узбецький національний ніж, колото-різана рана, шкіра, серце.



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Determination of the proliferative activity of the endometrium during the period of the implantation window in veteran women of reproductive age with a history of contusion

Serbeniuk A. V.

Shupik National Medical Academy of Postgraduate Education, Kiev, Ukraine

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CORRESPONDING AUTHOR

e-mail: anastasia.serbenyk@gmail.com
Serbeniuk A. V.

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Today, more than 50.000 women serve in the Armed Forces of Ukraine. The number of people with post-traumatic stress disorder is 27.7 % among military personnel who took part in active combat operations. Post-traumatic syndrome is a frequent predictor of various states of proliferative activity of the endometrium in veteran women of reproductive age with changes in the hormonal background, morphofunctional changes of the endometrium, which in turn negatively affects the reproductive health of women. The purpose of the work: to determine the proliferative activity of the endometrium in patients of reproductive age who took part in hostilities and suffered a concussion. The selection criteria of the women included in the study were: the presence of contusion in the anamnesis, normospermia in the husband, the absence of pregnancy within a year after putting the main disease into remission, and unfulfilled reproductive plans. The age of the examined women ranged from 20 to 40 years. 457 women who took part in combat operations and suffered concussions were examined. The criterion for inclusion in the main group (O) was post-concussive syndrome as a consequence of a concussion sustained during hostilities. The number of examinees was 211 women. The criterion for inclusion in the comparison group (P) (n=246 women) was a concussion during combat operations, but the absence of post-concussion syndrome. The control group (K) included 30 civilian women without episodes of any trauma in the anamnesis. Clinical, instrumental and morphological research methods were used during the research. The most significant differences in the number of immunopositive endometrial cells in the state of proliferation and apoptosis were noted between groups P and O in chronic endometritis and simple atypical hyperplasia of the endometrium. Thus, in the structure of the endometrium of women with reproductive plans who participated in hostilities with episode of contusion in anamnesis, an increase in the proliferation processes in the glands and stroma of the endometrium against the background of intensification of the processes of apoptosis in the stroma and a decrease in the processes of apoptosis in the glands, which may interfere with the normal course of adhesion, was characteristic blastocysts and trophoblast invasions during implantation. **Keywords:** reproductive health, female veteran, post-concussion syndrome, hysteroscopy, immunohistochemistry, endometrial cell apoptosis.

Introduction

Over the past few years, the population of Ukraine has faced a number of traumatic events: large-scale coups, a change of power, annexation of territories, and war. All these events continue to have a negative impact on the daily life of all Ukrainians, causing constant anxiety, tension and frustration, as well as an increase in the frequency and severity of stress disorders [12].

However, the biggest shock was the beginning of the

active phase of the war in February 2022 in Ukraine. By its actions, the aggressor country provoked an increase in the numerical and physical strength of the Armed Forces of Ukraine. Today, more than 50,000 women serve in the Armed Forces of Ukraine. Today, precisely in connection with the armed conflict in Ukraine, the psycho-emotional state of the population has significantly worsened. Military personnel develop post-traumatic stress disorder (PTSD)

under the influence of a combination of factors they encounter on the battlefield [12, 26].

Against the background of stress and post-traumatic stress disorder, changes in the hormonal background and morphofunctional changes of the endometrium occur in female military personnel [3, 7, 8, 9]. Among patients of reproductive age with infertility, hyperplastic processes of the endometrium are detected with a frequency of up to 50 % of cases, and they lead to reproductive function disorders [6, 14, 24, 25]. The mechanism of apoptosis processes remains relevant for decades and plays a leading role in the functioning of the female reproductive system; bc1-2 determines the mechanism of cell death, inhibiting apoptosis [2]. During the menstrual cycle (MC), endometrial cell death by apoptosis and their regeneration occur in a strictly regulated sequence and depend on the stage of the cycle [10, 13, 16, 18].

There is an opinion that disruption of apoptosis processes is of fundamental importance in hyperproliferative processes and cancerous regeneration of cells [12, 17, 19, 21]. Determining the signs that indicate a violation of cell death at the stage of endometrial hyperplasia can make it possible to predict the adverse course of the disease in a timely manner and choose the optimal individual treatment tactics aimed at preserving and restoring the generative function in women of reproductive age and preventing malignancy [7, 11, 19, 20]. Obviously, the need to increase the efficiency of diagnosis and treatment of endometrial pathology, to study the proliferative activity of the endometrium during the period of the implantation window in female military personnel of reproductive age becomes clear.

The purpose of the work: to determine the proliferative activity of the endometrium in patients of reproductive age with a concussion episode in the anamnesis.

Materials and methods

The study was conducted on the basis of the Department of Obstetrics, Gynecology and Reproductive Medicine and in the Department of Family Planning and Assisted Reproductive Technologies (DRT) with the office of endocrine gynecology and the day hospital of the Reproductive Technologies Clinic of the Ukrainian State Institute of Reproductive Medicine of the National University of Health Protection (NUOZ) of Ukraine named after P. L. Shupyka. The decision to approve the conduct of this clinical study was made at a meeting of the commission on bioethics of the P. L. Shupyka Protocol No. 8 dated June 7, 2021.

They studied the proliferative activity of the endometrium during the implantation window [1] in 487 women of reproductive age from 20 to 40 years. Controls were 30 conditionally healthy civilian women of reproductive age without any trauma episodes in the anamnesis. 457 women with a history of concussion were selected for the study. All women underwent hysteroscopy followed by

endometrial sampling for histological examination and scanning electron microscopy on the 21st day of the menstrual cycle. Thus, 457 women were divided into 2 groups - the main (O) group (211 women) and the comparison group (P) (246 women). Women of reproductive age with a history of trauma without post-concussion syndrome were included in the comparison group, and those women of reproductive age who had consequences of concussion in the form of post-concussion syndrome were separated into the main group. The average age of the examined was 37.08 ± 4.23 years. The period of stay in the hot spot was 60.26 ± 42.21 months, and from the moment of traumatic brain injury was 18.81 ± 9.22 months.

Complaints, gynecological, obstetrical, somatic, allergic and infectious anamnesis of the examined patients were studied in detail. The condition of the external and internal genitals was evaluated during a gynecological bimanual examination and examination of the cervix in mirrors.

Instrumental examination of women included hysteroscopy. All women underwent liquid hysteroscopy according to the standard technique. A 5 % glucose solution was used as a liquid medium. All the walls of the uterine cavity, the area of the eyes of the fallopian tubes were examined in turn, ending with an examination of the cervical canal. The color and thickness of the endometrium, its correspondence to the day of the menstrual cycle, the shape and size of the uterine cavity, the presence of pathological formations and inclusions, the relief of the walls, the condition of the mouth of the fallopian tubes were evaluated [23, 24]. A targeted biopsy of endometrial pathology was performed, then the rest of the endometrial cavity was evacuated using the "cold loop" method.

Proliferative activity was studied using the immunohistochemical (IGH) method of determining Ki-67 [15, 16]. For IGC studies, sections were placed on Super Frost Plus (Menzel, Germany) glass coated with adhesive. In order to "unmask" antigens, the sections were previously rehydrated and thermally treated with Target Retrieval Solution ("DAKO", Denmark) in a "Samsung CE118KFR" oven. The protein block affected the binding of non-specific proteins ("DAKO", Denmark), and the peroxidase block affected its endogenous activity ("DAKO", Denmark). After that, primary antibodies were applied. We worked with rabbit monoclonal antibodies (MAT) to Ki-67 (clone SP6, Thermo Scientific). The DAKO Advance polymer detection system visualized the primary antibodies. Horseradish DAB + (DAKO) was the substrate for peroxidase. As a result, the nuclei of the proliferation cells turned brown. The material was stained with Mayer's hematoxylin, followed by mounting in semi-synthetic Permanent Mounting Medium ("DAKO", Denmark).

The "ApopTag plus Peroxidase In Situ Apoptosis Detection Kit" manufactured by "Chemicon/Millipore" (USA) was used to detect cells undergoing apoptosis. This method is based on the TUNEL method, i.e. detection of

defragmented sections of DNA of apoptotic cells [17]. These areas were determined using the enzyme terminal deoxynucleotidyltransferase, which "stitched" modified oligonucleotides labeled with horseradish peroxidase to free 3'OH groups at the sites of DNA fragmentation. As a result of this interaction, stable complexes of labeled oligonucleotides with the end regions of fragmented DNA were formed, which were then visualized with the help of DAB-chromogen. Thus, the nuclei of cells that were in the process of apoptosis acquired a brown color. To visualize the histological structure of the examined tissue, the treated sections were stained with methyl green. Positively stained cells were counted in three fields of view and the percentage of positive cells in relation to all cells was calculated. The calculation was carried out for a minimum of 1000 cell elements.

Indicators of the level of bcl-2 expression in the endometrium were determined by the immunohistochemical method using monoclonal antibodies of the "DAKO" system (Denmark) - according to the manufacturer's instructions. Deparaffinized and rehydrated sections were studied. Unmasking of antigens in sections was performed by thermal induction of epitope retrieval (HIER) by immersing tissue preparations in Target Retrieval Solution ("DAKO", Denmark) reducing buffer and heating them for 15-20 minutes in the above oven. This procedure ensured the restoration of the structure of antigens before immunostaining. After blocking non-specific binding of proteins with a protein block ("DAKO", Denmark) and endogenous peroxidase activity with peroxidase ("DAKO", Denmark), unlabeled primary antibodies were applied. Mouse monoclonal antibodies to bcl-2 (clone 124, DAKO) were used. Primary antibodies were visualized using the DAKO CSA II Biotin-free Tyramide Signal Amplification System detection system. DAB + (DAKO) was used as a substrate for horseradish peroxidase. To visualize the histological structure of the examined tissue, the treated immunohistochemical preparations were stained with Mayer's hematoxylin. Next, the stained sections were placed in Canadian balsam. Lymph node tissue was used as a positive control. The negative control glass was incubated with antibody dilution fluid ("DAKO", Denmark) without the use of primary antibodies. Interpretation of the results of immunohistochemical staining with antibodies to bcl-2 was carried out taking into account the fact that this marker has a cytoplasmic nature of staining. Positive reactions were counted according to the number of cells that reacted (expressed as a percentage of the total number of cells on the area of the histological preparation) taking into account the intensity of staining. The optical intensity of staining was determined subjectively, it contained 4 gradations: 0 - no staining, 1 - weak staining, 2 - staining of medium intensity, 3 - intense staining. The percentage of positively stained cells varied from 0 to 100. The number of immunopositive cells under microscopy was counted in

three fields of view at a microscope magnification of x300. Next, the immunoreactivity index was calculated according to the formula: $Hscore = 1 \times (P1) + 2 \times (P2) + 3 \times (P3)$, where Hscore is the immunoreactivity index; P1, P2 and P3 are the percentages of positively stained cells with the corresponding staining intensity.

All morphometric studies were performed on an Olympus AX70 Provis microscope (Olympus, Japan) using the image analysis program Analysis 3.2 Pro (Soft Imaging, Germany), following all device recommendations.

The obtained results were processed on an IVM PC computer using the "Statistica 6.0" and Biostat software package, as well as analytical statistics methods: using the sampling method, the parameters of the general population were estimated based on sample data; statistical criteria were used to determine the validity of the proposed hypotheses: the t-test was used to compare the average values of independent samples and connected (dependent) samples; χ^2 -criterion - for analyzing the conjugation of features, comparing event frequencies; correlation analysis - to study stochastic dependence between indicators.

Results

In all examined women, the state of apoptosis and proliferation in the endometrium was studied on the 21st day of the menstrual cycle. When assessing cell proliferation in the control group by determining the nuclear antigen Ki-67, the presence of proliferation was revealed both in the stroma (0.261±0.072 %) and in the endometrial glands (0.031±0.022 %, $p < 0.002$) (Fig. 1, Table 1).

Apoptosis processes during the period of the implantation window in women of the control group prevailed over proliferation phenomena. The number of apoptotic cells according to the results of the TUNEL method in the stroma (4.677±0.272 %) (see Table 1)

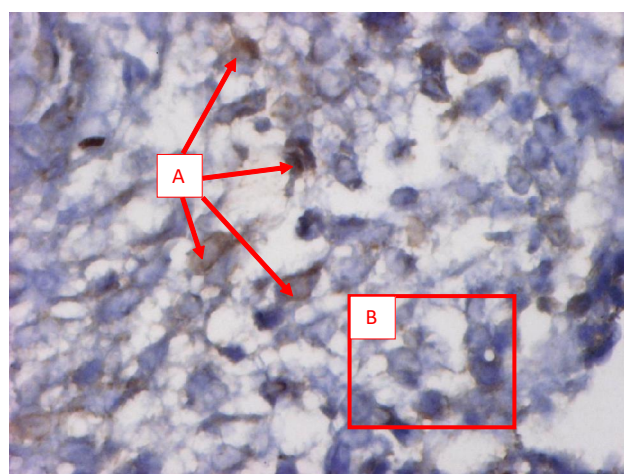


Fig. 1. Cells immunopositive for Ki-67 in the stroma of the endometrium on the 21st day of MC in a woman of the control group. A - cells immunopositive for Ki-67; B - endometrial stroma. IGH-staining with MAT to Ki-67, x400.

Table 1. The number of immunopositive endometrial cells in the state of proliferation and apoptosis in all examined groups (M±m, %).

- Morphofunctional state of the endometrium	The number of immunopositive cells with IHC-staining of MAT to Ki-67		The number of cells in the state of apoptosis when using the TUNEL method		Hscore to bcl-2 in the endometrium
	Stroma	Glands	Stroma	Glands	
Control group (n=30)					
Endometrium in the middle phase of secretion (n=30)	0.262±0.071	0.035±0.021	4.677±0.272	2.462±0.248	76.64±1.55
A group of women with a history of concussion (n=457)					
Endometrium with morpho-functional mismatch of the MC phase (n=65)	4.993±0.152 ^c	16.51±0.63 ^c	1.409±0.466 ^c	0.472±0.141 ^c	102.1±4.7 ^c
- in the proliferation phase (n=32)	5.302±0.195 ^c	17.49±1.09 ^c	0.939±0.602 ^c	0.072±0.057 ^c	105.7±5.7 ^c
- in the phase of early secretion (n=33)	4.704±0.231 ^c	15.55±0.61 ^c	1.864±0.712 ^c	0.854±0.261 ^c	98.52±7.52 ^c
The endometrium is in the middle phase of secretion, corresponding to the phase and period of MC (n=30)	4.126±0.281 ^c	0.202±0.091	5.437±0.514	1.182±0.328 ^c	93.51±9.95
Endometrium in the middle phase of secretion + chronic endometritis (n=50)	6.983±0.670 ^c	2.011±0.654 ^c	7.122±0.861 ^c	0.423±0.159 ^c	114.7±8.8 ^c
Endometrium in the middle phase of secretion + simple atypical hyperplasia of the endometrium (n=35)	5.453±0.471 ^c	3.527±1.041 ^c	7.386±1.011 ^c	0.615±0.183 ^c	97.24±8.28 ^c
Endometrium in the middle phase of secretion + polyp (n=34)	4.957±0.631 ^c	7.492±1.579 ^c	8.401±0.632 ^c	0.914±0.259 ^c	163.4±6.3 ^c

Notes: ^c - the difference is probable with a similar indicator of the control group (p<0.05).

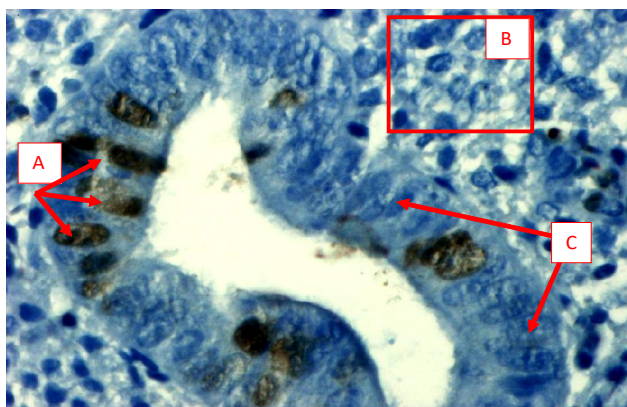


Fig. 2. Cells immunopositive for Ki-67 in the endometrial glands in an endometrial sample corresponding to the 21st day of MC proliferation phase in a female patient of reproductive age who participated in combat operations and suffered a contusion. A - cells immunopositive for Ki-67, B - endometrial stroma; C - endometrial glands. IGH-staining with MAT to Ki-67, x400.

exceeded that in the glands (2.462±0.248 %) by 1.9 times (p<0.001). A direct correlation was established between the number of Ki-67 immunopositive cells and the number of cells in the state of apoptosis in the endometrial stroma when using the TUNEL method (r=0.67, p<0.001). The study of the bcl-2 proto-oncogene, which blocks apoptosis, showed that the Hscore for bcl-2 in the endometrium was 76.64±1.55 %. IGH staining of MAT cells for bcl-2 was exclusively cytoplasmic and was observed during the implantation window in cells of the glandular epithelium, in fibroblasts of the stroma and, especially, in lymphoid follicles.

In the patients of the studied groups with a morpho-

functional mismatch of the endometrium phase and day of the MC, more pronounced proliferation and less pronounced apoptosis was observed in the glandular epithelium and stroma of the functional layer of the uterine mucosa compared to controls. Thus, in endometrial samples corresponding to the proliferative phase of MC on the 21st day, the number of Ki-67 immunopositive cells in the stroma exceeded that in the control by 15.7 times (p<0.001) (Fig. 2), in the glandular epithelium by 5.8 times (p<0.001), Hscore to bcl-2 was 1.2 times more (p<0.001), and the number of cells in the state of apoptosis in the

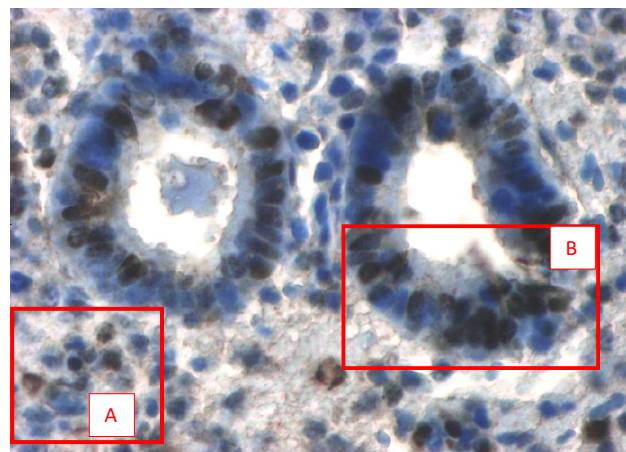


Fig. 3. Ki-67-immunopositive cells in the endometrial stroma and glands in an endometrial sample corresponding to the 21st day of MC in the early phase of secretion in a patient of reproductive age who participated in combat operations and suffered a contusion. A - cells immunopositive for Ki-67 in the stroma of the endometrium; B - cells immunopositive for Ki-67 in the gland. IGH-staining with MAT to Ki-67, x300.

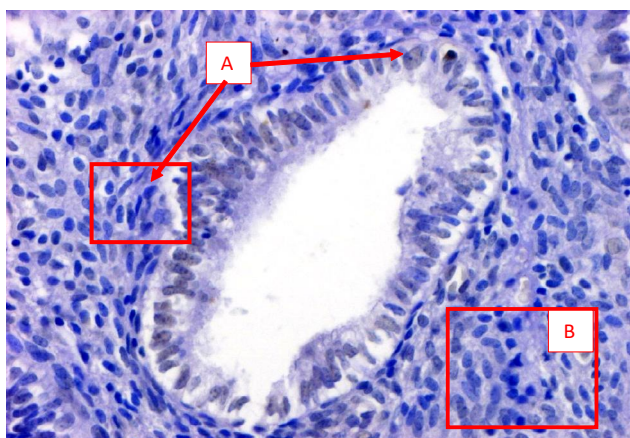


Fig. 4. Weakly expressed apoptosis in the endometrium in the endometrial sample corresponding to the 21st day of MC in the early phase of secretion in a patient of reproductive age who participated in combat operations and suffered a contusion. A - mild apoptosis in the endometrial gland; B - endometrial stroma. TUNEL method, x150.

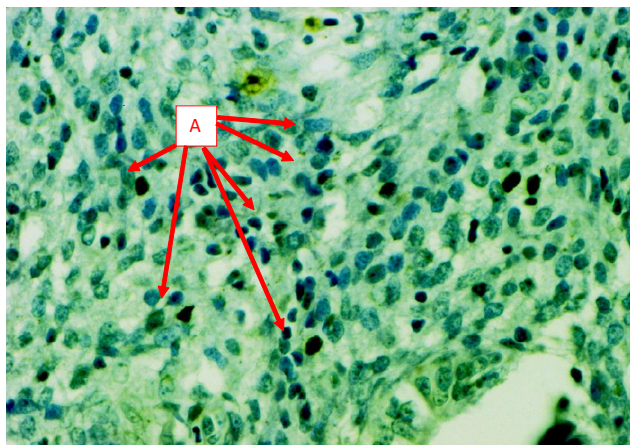


Fig. 5. Apoptosis in the endometrial stroma in an endometrial sample corresponding to the 21st day of MC in the middle phase of secretion in a patient of reproductive age who took part in combat operations and suffered a contusion. A - Pronounced apoptosis in the stroma of the endometrium. TUNEL method, x150.

stroma was 1.2 times less ($p < 0.001$), in the glands - 2.1 times ($p < 0.001$).

In women of reproductive age who took part in hostilities and suffered a contusion with endometrial correspondence on the 21st day of MC phase of early secretion, the number of immunopositive cells to Ki-67 in the stroma exceeded that in the control by 17.9 times ($p < 0.001$), in the glands - 44.2 times ($p < 0.001$) (Fig. 3). Hscore to bcl-2 was 1.3 times higher ($p < 0.007$), and the number of cells in the state of apoptosis (Fig. 4) was 2.5 times lower in the stroma ($p < 0.001$), and 2.9 times lower in the glands ($p < 0.001$).

In patients of reproductive age who took part in combat operations and suffered a contusion with morphofunctional conformity of the endometrium on the 21st day of MC in the middle phase of secretion, probable differences from women of the control group were an increase in the number

of immunopositive cells to Ki-67 in the stroma of the endometrium by 15.7 times ($p < 0.001$) and a decrease in the number of cells in the state of apoptosis in the glands by 2.1 times ($p < 0.003$). The number of immunopositive cells in the IHC staining of MAT to Ki-67 in the glands, the number of cells in the state of apoptosis when using the TUNEL method (Fig. 5) and Hscore to bcl-2 had no significant differences with the control indicators.

Active proliferation of cells in the stroma (26.8 times higher than in the control, $p < 0.001$) and in the glands (67.0 times higher than in the control, $p < 0.004$) was found in women whose endometrium corresponded to the middle phase of secretion. At the same time, the ratio of proliferating cells in the stroma exceeded that in the glands by 20.4 times ($p < 0.001$) (Fig. 6). Similarly, the number of cells in the state of apoptosis in the stroma exceeded that in the glands by 4.6 times ($p < 0.001$).

Compared to the control, the level of apoptosis in the

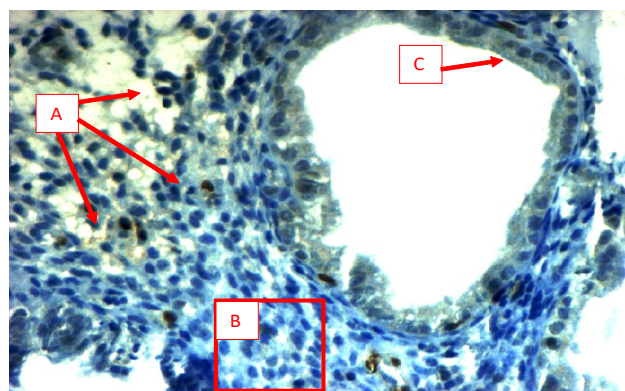


Fig. 6. Cells immunopositive for Ki-67 in the endometrium with symptoms of chronic endometritis in a sample corresponding to the 21st day of MC in the middle phase of secretion in a patient of reproductive age who participated in combat operations and suffered a contusion. A - cells immunopositive for Ki-67, B - endometrial stroma, C - endometrial gland. IGH-staining with MAT to Ki-67, x150.

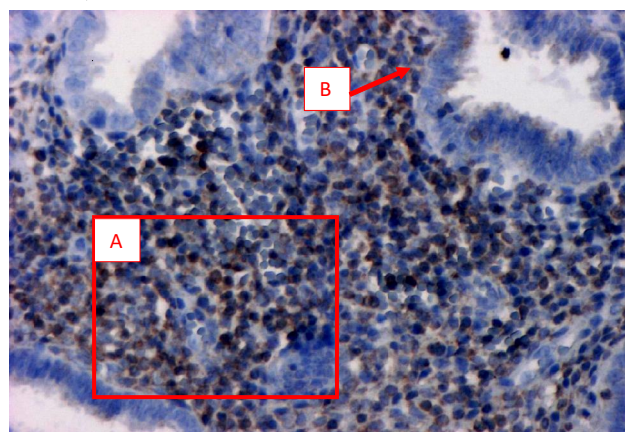


Fig. 7. Increased expression of bcl-2 in lymphohistioplasmacytic infiltrates in chronic endometritis on the 21st day of MC in a patient of reproductive age who participated in combat operations and suffered a contusion. A - expression of bcl-2 in the stroma of the endometrium, B - endometrial gland. IGH with MAT to bcl-2, x150.

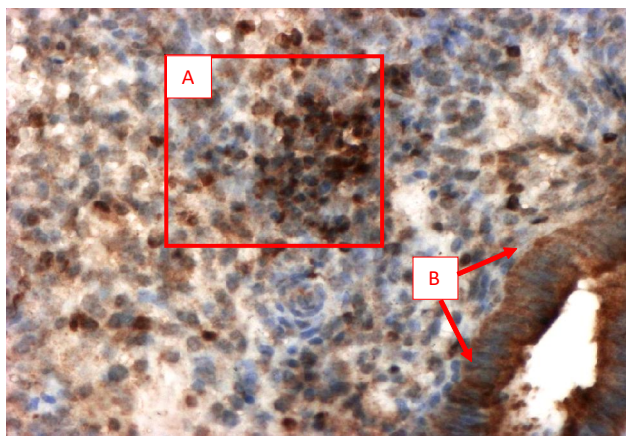


Fig. 8. High level of bcl-2 expression in glands and endometrial stroma around a polyp in an endometrial sample corresponding to the 21st day of MC in the middle phase of secretion in a female patient of reproductive age who participated in combat operations and suffered a contusion. A - expression of bcl-2 in the stroma of the endometrium, B - expression of bcl-2 in the endometrial gland. IGH with MAT to bcl-2, x190.

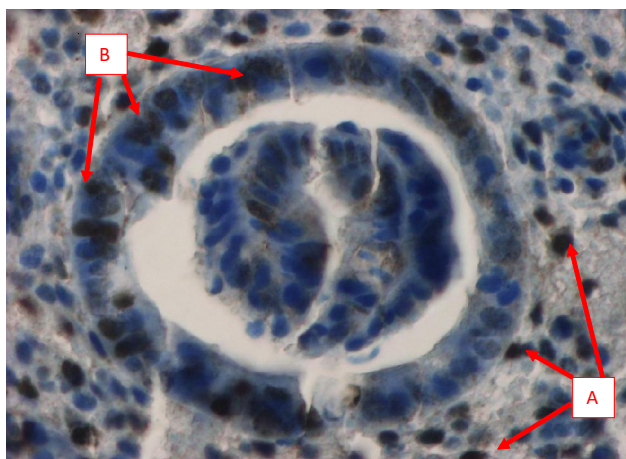


Fig. 9. Cells immunopositive for Ki-67 in the stroma and endometrial gland with PNGE on the 21st day of the menstrual cycle in a female patient of reproductive age who participated in combat operations and suffered a contusion. A - cells immunopositive for Ki-67 in the stroma of the endometrium; B - cells immunopositive for Ki-67 in the endometrial gland. IGH-staining with MAT to Ki-67, x300.

stroma was 1.5 times higher ($p < 0.001$), and in the glands - 5.9 times lower ($p < 0.001$). Hscore to bcl-2 in the endometrium exceeded that in the control by 1.5 times ($p < 0.001$) (Fig. 7).

The endometrium surrounding the polyps was characterized by an increase in the number of Ki-67 immunopositive cells in the stroma by 18.9 times, in the glands by 249.7 times ($p < 0.001$), as well as the number of cells in a state of apoptosis in the stroma by 1.6 times ($p < 0.001$).

A distinctive feature of the condition of the endometrial glands surrounding the polyp was a 2.7-fold decrease in the number of apoptotic cells compared to the control ($p < 0.001$). Accordingly, the Hscore for bcl-2 in the

endometrium surrounding the polyp was increased by 2.1 times ($p < 0.001$) (Fig. 8).

In the endometrium in the middle phase of secretion with PNGE phenomena in the stroma, the number of cells in the state of apoptosis was 1.6 times ($p < 0.001$) greater than that in the state of proliferation, and in the glands, on the contrary, the number of cells in the state of proliferation was 5.8 times greater than that in the state of apoptosis ($p < 0.001$). Compared to the control, the number of Ki-67 immunopositive cells in the stroma was 20.7 times higher ($p < 0.001$), in the glands - 100.7 times ($p < 0.002$) (Fig. 9), the number of cells in the state of apoptosis in the stroma was 1.9 times higher times ($p < 0.01$), the Hscore to bcl-2 was 1.3 times higher ($p < 0.02$), and the number of cells in the state of apoptosis in the glands was 4.0 times less ($p < 0.001$). A decrease in the processes of apoptosis in the glands in PNGE was accompanied by an increase in the expression of bcl-2 in the glands compared to the stroma (Fig. 10), and in some cases, the presence of bcl-2 expression only in the glands.

Analysis of the number of immunopositive cells of the endometrium in a state of proliferation and apoptosis in women of reproductive age who took part in combat operations and suffered a contusion during the period of the implantation window, depending on the presence of post-concussion syndrome (Table 2) showed that in all investigated morphofunctional states of the endometrium, the content in endometrial stroma of Ki-67 immunopositive cells and bcl-2 in the endometrium of women with post-concussion syndrome was greater than that of patients without post-concussion syndrome in the endometrium, which corresponds to the proliferation phase - by 20.2 ($p < 0.001$) and 1.4 times ($p < 0.001$), in the endometrium, which corresponds to the phase of early secretion, in 17.9 ($p < 0.001$) and 1.9 times ($p < 0.001$), in the endometrium

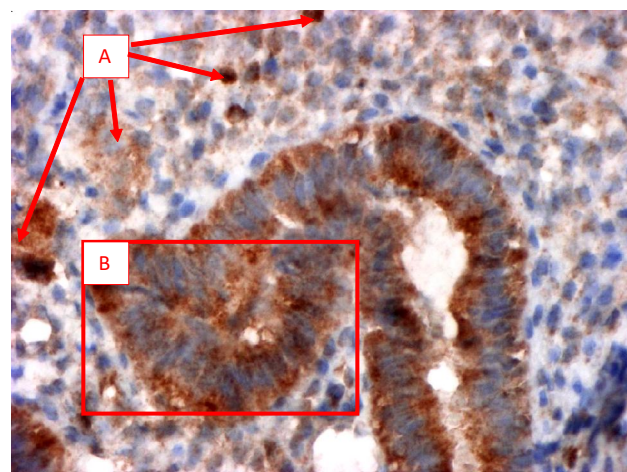


Fig. 10. Expression of bcl-2 by cells of endometrial glands, stroma, and lymphoid elements in the stroma of the endometrium with PNGE on the 21st day of MC in a patient of reproductive age who participated in combat operations and suffered a contusion. A - expression of bcl-2 in the stroma of the endometrium, B - expression of bcl-2 in the endometrial gland. IGH with MAT to bcl-2, x225.

Table 2. The number of immunopositive cells of the endometrium in the state of proliferation and apoptosis in all groups of women (M±m, %).

Morphofunctional state of the endometrium	Group	The number of immunopositive cells with IHC-staining of MAT to Ki-67		The number of cells in the state of apoptosis when using the TUNEL method		Hscore to bcl-2 in the endometrium
		Stroma	Glands	Stroma	Glands	
Control group (n=30)						
Endometrium in the middle phase of secretion (n=30)		0.261±0.072	0.035±0.021	4.673±0.274	2.461±0.243	76.64±1.556
Women with a history of concussion (n=457)						
Endometrium in the phase of proliferation (n=32)	O, n=17	6.001±0.225 ^{c,p}	21.83±1.18 ^{c,p}	0.722±0.719 ^c	0.000±0.000 ^c	129.4±5.502 ^p
	P, n=15	4.514±0.143 ^{c,o}	12.58±0.74 ^{c,o}	1.164±1.021 ^c	0.152±0.101 ^c	78.94±4.012 ^o
The endometrium corresponds to the phase of early secretion (n=33)	O, n=17	5.642±0.285 ^{c,p}	18.53±0.35 ^{c,p}	1.664±1.003 ^c	0.743±0.331 ^c	128.2±9.306 ^{c,p}
	P, n=16	3.701±0.106 ^{c,o}	12.39±0.47 ^{c,o}	2.081±1.034 ^c	0.974±0.413 ^c	67.01±4.801 ^o
Endometrium in the middle phase of secretion (n=30)	O, n=15	5.334±0.312 ^{c,p}	0.365±0.173 ^c	7.641±0.523 ^{c,p}	0.741±0.335 ^c	114.1±14.41 ^{c,p}
	P, n=15	2.901±0.116 ^{c,o}	0.041±0.016	3.227±0.354 ^{c,o}	1.619±0.554	72.91±11.86 ^o
Endometrium in the middle phase of secretion + chronic endometritis (n=50)	O, n=25	10.52±0.801 ^{c,p}	2.509±1.002 ^c	10.08±1.245 ^{c,p}	0.337±0.192 ^c	169.1±7.17 ^{3c,p}
	P, n=25	3.441±0.412 ^{c,o}	1.524±0.847	4.178±0.861 ^{c,o}	0.517±0.254 ^c	60.24±4.421 ^{c,o}
Endometrium in the middle phase of secretion + simple atypical hyperplasia of the endometrium (n=35)	O, n=18	7.689±0.778 ^{c,p}	9.723±2.451 ^c	11.00±0.77 ^{c,p}	0.511±0.278 ^c	193.5±2.9 ^{06c,p}
	P, n=17	2.065±0.163 ^{c,o}	5.127±1.849 ^c	5.657±0.351 ^{c,o}	1.331±0.413 ^c	131.6±6.5 ^{c,o}
Endometrium in the middle phase of secretion + polyp (n=34)	O, n=17	7.468±0.492 ^{c,p}	4.812±1.749 ^c	11.22±1.19 ^{c,p}	0.482±0.235 ^c	136.6±6.7 ^{c,p}
	P, n=17	3.433±0.432 ^{c,o}	2.244±1.101	3.534±0.971 ^o	0.744±0.283 ^c	57.88±6.71 ^{c,o}

Notes: ^{c, o, p} - the difference is likely with a similar indicator of groups O, P and control (p<0.05).

corresponding to the middle phase of secretion - in 15.7 (p<0.001) and 1.2 times (p<0.04), in chronic endometritis - in 26.6 (p<0.0001) and 1.5 times (p<0.001), with simple atypical endometrial hyperplasia - 20.8 (p<0.001) and 1.3 times (p<0.001), with endometrial polyps - 18.9 (p<0.001) and 2.1 times (p<0.001). Also, in women with post-concussion syndrome, Ki-67 immunopositive cells were significantly more often recorded in the glands of the endometrium corresponding to the proliferation phase - 6.2 times (p<0.001) and in the endometrium corresponding to the early secretion phase - 5.3 times (p<0.001).

In the women of the main group, compared to the patients of the P group, apoptotic cells were found in the stroma of the endometrium when using the TUNEL method: in the endometrium in the middle phase of secretion by 20.4 times, in chronic endometritis by 40.3 times (p<0.001), in simple atypical endometrial hyperplasia (PNHE) - 2.9 times (p<0.001), with endometrial polyps - 2.9 times (p<0.001).

Discussion

According to data from international studies, the beginning of apoptosis in the glands and stroma is preceded by a decrease in the concentration of E2 and P in blood serum, while the increase in the apoptotic index in the stroma is delayed by 2 days compared to the endometrial glands. A decrease in the number of receptors

for estrogens-? and P in the uterine epithelium correlates with an increase in the apoptotic index in it. The intensity of apoptosis processes increases 3-5 days after the P peak in the middle of the luteal phase, then the process gradually spreads to all cellular components of the functional layer, reaching the maximum level 2 days before the onset of menstruation. Cells of the basal layer do not undergo apoptosis in any of the stages of the menstrual cycle [5, 25].

Over the past 20 years, active research conducted in high-tech countries of the world has proven the leading role of apoptosis inhibitors, which are the bcl-2 family of oncogenes [22], increased production of gonadotropic hormones (FSH and LH), their disordered secretion, accumulation of somatic cell mutation factors, aging of the body, metabolic disorders (oxidative stress), etc. [7]. Also, according to the data of foreign literature, the opposite effect of the regulation of apoptosis by the same hormone has been proven, depending on the stage of cell differentiation. Thus, estrogens are inhibitors of apoptosis of the uterine epithelium at the beginning of MC and an inducer at the end. The inhibitor of apoptosis of the glandular epithelium of the uterus at the end of the cycle is P [4, 18, 19].

Research conducted in 2019 by the group of authors L. Craciunas and co-authors noted that the increased expression of genes that are inhibitors of apoptosis and inducers of proliferation increases the proliferative activity

of biologically inappropriate cells, gives them increased stability, extraordinary survival, and resistance to self-destruction [5]. During the proliferative and early secretion phase, apoptosis is low, which has profound physiological meaning. In the late stage of proliferation, the expression of the inhibitor of apoptosis (bcl-2 inhibitor gene) decreases as much as possible, which enhances the apoptotic self-destruction of virus-infected, damaged, biologically inappropriate endometrial cells, including those with high proliferative potential. Apoptosis, as a physiological process, has a protective nature [9, 18, 21].

Also, attention is drawn to the data published in world sources that during the period of implantation, the proliferative and mitotic activity of the cells of the glandular epithelium increases, which correlates with the increasing concentration of E2. The secretory activity of the glands reaches a maximum. Characteristic morphological changes of the endometrial glands, observed only in the secretory phase, include the appearance of giant mitochondria, glycogen deposition, and the formation of nuclear channel systems [10, 14].

As can be seen from the data we obtained, the most significant differences in the number of immunopositive endometrial cells in the state of proliferation and apoptosis were noted between groups P and O in chronic endometritis and simple atypical endometrial hyperplasia (PNHE). The endometrium of women of reproductive age who took part in hostilities and suffered a contusion during the implantation window is characterized by increased proliferation processes in the glands and stroma of the endometrium against the background of intensification of apoptosis processes in the stroma and a decrease in apoptosis processes in the glands, which can interfere with the normal course of blastocyst adhesion and trophoblast invasion during implantation. A decrease in the apoptotic activity of the endometrial glands is carried out against the background of increased expression of the bcl-2 inhibitor of apoptosis, mainly in the endometrial glands and lymphohistioplasmacytic infiltrates. Violation of the intensity and relationship of the processes of proliferation and apoptosis leads not only to a violation of the morphofunctional state of the endometrium, but also to the formation of polyps and hyperplasia of the endometrium in women of reproductive age who took part in combat operations, which must be taken into account during the pre-gravid preparation of such patients.

The content in the endometrial stroma of immunopositive cells for Ki-67 and bcl-2 in the endometrium of women with post-concussion syndrome was greater than that of patients without post-concussion syndrome: in the endometrium, which corresponds to the proliferation phase, by 1.4 ($p < 0.001$) and by 1.6, respectively times ($p < 0.001$), in the endometrium corresponding to the phase of early secretion - in 1.5 ($p < 0.0001$) and 1.9 times ($p < 0.001$), in the endometrium corresponding to the middle phase of secretion - in 1.8 ($p < 0.001$) and 1.6 times ($p < 0.04$), with chronic endometritis - 3.1 ($p < 0.001$) and 2.8 times ($p < 0.0001$), with simple atypical endometrial hyperplasia - 3.7 ($p < 0.001$) and 1.5 times ($p < 0.001$), with endometrial polyps - 2.2 times ($p < 0.001$) and 2.4 times ($p < 0.001$).

Conclusion

1. Apoptosis processes during the period of the implantation window in women of the control group prevailed over proliferation phenomena.

2. In the patients of the studied groups with morphofunctional mismatch of the endometrium to the phase and day of the menstrual cycle, more pronounced proliferation and less pronounced apoptosis in the glandular epithelium and stroma of the functional layer of the uterine mucosa were observed compared to controls.

3. Active proliferation of cells in the stroma and glands was found in women whose endometrium corresponded to the middle phase of secretion. At the same time, the ratio of proliferating cells in the stroma exceeded that in the glands by 3.5 times.

4. Reduction of apoptosis processes in the glands in simple atypical hyperplasia of the endometrium was accompanied by an increase in the expression of bcl-2 in the glands compared to the stroma, and in some cases by the presence of bcl-2 expression only in the glands.

5. The content in the stroma of the endometrium of immunopositive cells for Ki-67 and bcl-2 in the endometrium of women with post-concussion syndrome was greater than that of patients without post-concussion syndrome: in the endometrium corresponding to the proliferation phase - by 1.4 and 1.6 times, respectively, in endometrium corresponding to the phase of early secretion - 1.5 and 1.9 times, in endometrium corresponding to the middle phase of secretion - 1.8 and 1.6 times, with chronic endometritis - 3.1 and 2.8 times, with PNHE - 3.7 and 1.5 times, with endometrial polyps - 2.2 and 2.4 times.

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ВИЗНАЧЕННЯ ПРОЛІФЕРАТИВНОЇ АКТИВНОСТІ ЕНДОМЕТРІЯ У ПЕРІОД ВІКНА ІМПЛАНТАЦІЇ У ЖІНОК-ВЕТЕРАНІВ РЕПРОДУКТИВНОГО ВІКУ З КОНТУЗИЄЮ В АНАМНЕЗІ Сербенюк А. В.

На сьогоднішній день у лавах Збройних сил України служать понад 50000 жінок. Серед військовослужбовців, котрі брали участь в активних бойових діях, кількість осіб із посттравматичним стресовим розладом становить 27,7 %. Посттравматичний синдром є частим предиктором різних станів проліферативної активності ендометрія у жінок-ветеранок репродуктивного віку зі змінами гормонального фону, морфофункціональними змінами ендометрія, що в свою чергу негативно впливає на репродуктивне здоров'я жінок. Мета роботи: визначити проліферативну активність ендометрія у пацієнток репродуктивного віку з епізодом контузії в анамнезі. Критеріями відбору жінок, включених до дослідження, були: наявність контузії в анамнезі, нормоспермія у чоловіка, відсутність настання вагітності впродовж року після введення в ремісію основного захворювання та нереалізовані репродуктивні плани. Вік обстежених жінок був у межах від 20 до 40 років. Обстежили 457 жінок, котрі приймали участь у бойових діях та зазнали контузії. Критерієм включення до основної групи (О)

був постконтузійний синдром як наслідок перенесеної контузії під час бойових дій. Кількість обстежених становила 211 жінок. Критерієм включення до групи порівняння (Р) (n=246 жінок) була перенесена контузія під час бойових дій, але відсутність постконтузійного синдрому. До контрольної групи (К) увійшли 30 цивільних жінок без епізодів будь-якої травми в анамнезі. Під час дослідження були використані клінічні, інструментальні та морфологічні методи дослідження. Найбільш суттєві відмінності кількості імунопозитивних клітин ендометрія в стані проліферації та апоптозу відмічалися між групами Р і О при хронічному ендометриті і простій неатиповій гіперплазії ендометрія. Таким чином, у структурі ендометрія пацієнток репродуктивного віку, що брали участь у бойових діях та зазнали контузії, характерним було підвищення процесів проліферації в залозах і стромі ендометрія на фоні інтенсифікації процесів апоптозу в стромі і зниження процесів апоптозу в залозах, що може перешкоджати нормальному перебігу адгезії бластоцисти та інвазії трофобласта під час імплантації.

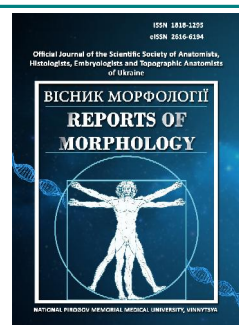
Ключові слова: репродуктивне здоров'я, жінка-ветеранка, постконтузійний синдром, гістероскопія, імуногістохімія, апоптоз клітин ендометрія.



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Correlational relationships of intestinal wall parameters after barotrauma

Kosharniy V. V., Abdul-Ogli L. V., Kozlov S. V., Rutgaizer V. G., Rutgaizer O. A.

Dnipro State Medical University, Dnipro, Ukraine

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CORRESPONDING AUTHOR

e-mail: kosha.v@ukr.net

Kosharniy V. V.

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Explosions are physical phenomena that lead to a sudden release of energy; they can be chemical, nuclear or mechanical. This process results in an almost instantaneous increase in pressure above atmospheric pressure. Damage to the abdominal organs after the action of explosion factors (shock blast wave, striking elements of the explosive device, secondary shells, chemical and thermal factors) is a fairly common clinical situation. The small and large intestines are the most vulnerable to the impact of a shock blast among the abdominal organs. The aim of the study was a study of the distant consequences of the influence of barotrauma on the morphometric parameters of the intestines of white rats and their correlations. The studies were performed on 20 white outbred sexually mature rats weighing 180-200 g. The wall of the small intestine was stained with hematoxylin and eosin according to the generally accepted method. The thickness of the entire intestinal wall, mucous, muscular and serous membranes, the length and width of the villi, the depth and width of the crypts were determined. Statistical processing of morphometry results was performed using the Statistica 10.0 program. Analysis of histopathological changes in the wall of the small intestine by light microscopy on the seventh day after the impact of the shock air wave on the anterior abdominal wall showed a significant thickening of the mucous membrane, submucosa, muscle membrane compared with the control group of animals. Thickening of the intestinal wall layers occurred due to intercellular edema and edema of stromal elements. At the time of the study, an inflammatory reaction with predominantly neutrophilic infiltration was present in all mucosal, submucosal, and muscular membranes. From the vascular bed in the vessels of the mucous and submucosal membranes, circulatory disorders occurred in the form of plethora and stasis in the vessels of various diameters and affiliations. Thickening of the layers of the intestinal wall occurred due to intercellular edema, swelling of stromal elements. The analysis of the morphometric parameters of the wall of the small intestine showed that in experimental rats after barotrauma simulation, quantitative changes occur at both the cellular and tissue levels, which correlate with the observation period. The muscular shell is subject to more pronounced changes under the action of a shock wave, which is confirmed by morphometric studies and correlation analysis. When conducting a correlation analysis, it was established that all indicators had strong positive relationships with each other, except for the parameter of the thickness of the muscle layer. Changes in the average thickness of the mesenteric layer had a moderate relationship with all parameters except crypt width and mucosal thickness.

Keywords: digestive tube, morphology, barotrauma, intestinal wall, morphometry, correlation analysis.

Introduction

Explosions are physical phenomena that lead to a sudden release of energy; they can be chemical, nuclear or mechanical. This process results in an almost instantaneous increase in pressure above atmospheric pressure. The increase in positive pressure compresses

the environment and leads to the propagation of a blast wave that spreads radially outward from the explosion site. As the leading edge of the blast wave expands, after the positive phase the pressure decreases and a negative wave develops before further returning to the ascending

level [3]. Explosions generate blast waves that are not necessarily caused by explosives. A blast wave consists of two parts: a shock wave and blast wind [14]. "Primary" blast injuries are caused by the direct interaction of the blast wave with the human body, especially with damage to organs containing air. In the experimental study of the mechanisms of blast wave action, significant test results depend on the corresponding simulated conditions [5].

Damage to the organs of the abdominal cavity after the action of explosion factors (shock blast wave, striking elements of the explosive device, secondary projectiles, chemical and thermal factors) is a fairly widespread clinical situation [1, 8, 16, 18]. Among the organs of the abdominal cavity, the small and large intestines are the most vulnerable under the action of a shock blast wave. But closed explosion-induced traumatic injuries of internal organs are difficult at the stages of the diagnostic process, which is the reason for untimely provision of specialized medical care [15, 19]. The untimely detection of explosion-induced trauma to the organs of the abdominal cavity, in particular the intestines, leads to serious consequences, namely peritonitis, intra-abdominal bleeding, as a result of traumatic perforations and ruptures of intra-abdominal vessels [7, 12, 18]. This especially applies to low-intensity explosions, when a person does not pay due attention to it and does not consult a doctor.

Various diagnostic algorithms using ultrasound technology, special medical equipment (diagnostic laparoscopy), etc. are used to recognize intestinal injuries [6, 9, 17]. But this list, in the absence of a pathomorphological picture, does not allow detecting intestinal damage, which is formed at the ultra-, cellular- and tissue level. In recent years, various biomarkers of pathological processes have been actively introduced into the diagnostic program [6, 15, 18, 19]. But as for explosion-induced intestinal injuries, such diagnostic panels are not used.

The aim of the study was to study the long-term effects of barotrauma on the morphometric parameters of the intestines of white rats and their correlations.

Materials and methods

The research was carried out within the framework of the initiative scientific topic of the Department of Clinical Anatomy, Anatomy and Operative Surgery "Morphofunctional state of organs and tissues of experimental animals and humans in ontogenesis in normal and under the influence of external and internal factors", state registration number 0117U003181.

The research was carried out on 20 white outbred sexually mature rats weighing 180-200 g. During the entire period of preparation for the experiment and during its conduct, the rats were kept in the vivarium of the Dnipro State Medical University, at a temperature of 20-25°C, humidity of at least 50 %, in a well-ventilated room and according to the world day/night mode, in standard plastic

cages, no more than five animals in each with a standard diet: the daily requirement of an adult animal is on average 30-32 g (25 g of sour cream feed, 5-7 g of vegetables). All experimental rats were healthy and active. All animals were divided into three groups (control and two experimental). Rats of the control group were put under thiopental anesthesia and fixed. The experimental group included those rats that simulated abdominal barotrauma under thiopental anesthesia using a specially developed device (patent No. 146858 Ukraine, IPC G09B23/28, dated 24.03.2021). Rats were removed from the experiment 7 and 14 days after receiving abdominal barotrauma. The experiment was carried out in compliance with the rules of conducting work on experimental animals, with observance of the principles of humanity laid down in the directives of the European Community and the Declaration of Helsinki. All studies have been approved by the Bioethics Commission of the Dnipro State Medical University (Meeting Minutes No. 4 dated 24.11.2021).

Morphometry is one of the methods, thanks to which it is possible to objectify the data of cytological research. After the animals were removed from the experiment, a laparotomy was performed, the state of the small intestine was visually assessed, and its proximal section was removed for further pathohistological examination. The wall of the small intestine was stained with hematoxylin and eosin according to the standard method. The thickness of the entire intestinal wall, mucous, muscular and serous membranes, the length and width of the villi, the depth and width of the crypts were determined. Morphometry was performed in order to establish differences in morphometric parameters after barotrauma.

The research results were processed by mathematical and statistical methods. Differences between groups were determined by using Student's t-test. Statistical processing of morphometry results was performed using the Statistica 10.0 program (StatSoft Inc., USA). We used the arithmetic mean (\bar{x}) and standard errors (SE) to describe the degree of general trend of quantitative traits. The conclusion regarding the strength of the relationship between the studied parameters was made according to the following rule: if the correlation coefficient was equal to one, then the relationship is complete; if it is 0.7-0.9, then the connection is strong; if it is in the range of 0.5-0.7, then the connection is average, 0.2-0.5 the connection is weak, and less than 0.2 is very weak [2].

Results

The analysis of the morphometric parameters of the intestine showed that the experimental rats undergo changes in the intestinal wall after simulating barotrauma.

The average *length of the villi of the small intestine* of the control group was $275.9 \pm 1.1 \mu\text{m}$, in the first hour after barotrauma simulation it was $304.5 \pm 3.5 \mu\text{m}$, so the average length of the villi increased by 10.39 %. On the seventh day, the average indicator of the length of the villi was $295.4 \pm$

2.7 μm - the average length of the villi increased by 7.09 %. On the fourteenth day, the average length of the villi was $280.9 \pm 1.1 \mu\text{m}$ - an increase of the studied indicator relative to the similar indicator of the control group by 1.81 % was established. Thus, on the seventh day of the experiment, the average length of the villi of the small intestine relative to the first hour after barotrauma decreased by 2.99 %, and on the 14th day by 7.77 %.

The average value of the *small intestine villi width* of the control group was $75.53 \pm 0.69 \mu\text{m}$, and in the first hour after barotrauma simulation, this indicator was $82.62 \pm 1.67 \mu\text{m}$, that is, the average villus width increased by 9.23 %. On the seventh day, the average width of the villi was $80.65 \pm 1.85 \mu\text{m}$ - the value of the indicator of the average width of the villi increased by 6.78 %. On the fourteenth day, the value of the indicator of the average width of the villi was $77.53 \pm 0.57 \mu\text{m}$ - this indicator increased by 2.65 % compared to the similar indicator of the control group. Thus, on the seventh day of the experiment, the value of the indicator of the average width of the villi relative to the first hour after the barotrauma decreased by 2.40 %, and on the 14th day by 6.16 %.

The average value of the indicator of the *length of the small intestine crypts* of the control group was $258.5 \pm 0.5 \mu\text{m}$, and in the first hour after barotrauma simulation, it was $298.2 \pm 4.2 \mu\text{m}$. Therefore, the average value of the crypt length indicator increased by 15.34 %. On the seventh day, the average length of the crypts was $289.2 \pm 5.5 \mu\text{m}$ - the average length of the crypts of the small intestine increased by 11.87 %. On the fourteenth day, the average length of the crypts was $262.5 \pm 0.5 \mu\text{m}$. Therefore, the studied parameter increased by 1.55 % compared to the similar indicator of the control group. On the seventh day, the indicator of the average length of the crypts of the small intestine compared to the first hour after barotrauma decreased by 3.00 %, and on the 14th day by 12.00 %.

The average value of the indicator of the *width of the crypts of the small intestine* of the control group was $37.22 \pm 0.58 \mu\text{m}$; in the first hour after simulating barotrauma, this value was equal to $42.32 \pm 2.64 \mu\text{m}$. Therefore, an increase in the average value of the indicator of the width of the crypts of the small intestine by 13.70 % was established. On the seventh day, the value of the indicator of the average width of the crypts was $40.32 \pm 3.54 \mu\text{m}$, the studied parameter increased by 8.33 %. On the fourteenth day, the value of the indicator of the average width of the crypts of the small intestine was $36.22 \pm 0.54 \mu\text{m}$, the indicator we studied decreased by 2.69 % compared to the similar indicator of the control group. Thus, on the seventh day, the average width of the crypts decreased by 4.73 % compared to the first hour after barotrauma, and on the 14th day by 14.41 %.

The average value of the indicator of the *thickness of the wall of the small intestine* of the control group was $678.4 \pm 0.4 \mu\text{m}$, in the first hour after the simulation of barotrauma it was equal to $705.5 \pm 6.5 \mu\text{m}$, therefore, an increase of this indicator by 3.98 % was established. On the seventh day, this indicator was $698.5 \pm 7.4 \mu\text{m}$, so the

average wall thickness increased by 2.95 %. On the fourteenth day, the average value of the wall thickness of the small intestine was $680.4 \pm 0.4 \mu\text{m}$, so it increased by 0.29 % compared to the similar indicator of the control group. Thus, on the seventh day of the study, the average thickness of the wall of the small intestine, relative to the first hour after barotrauma, decreased by 0.99 %, and on the 14th day by 3.55 %.

The average value of the *thickness of the mucous membrane of the small intestine* of the control group was $538.3 \pm 4.3 \mu\text{m}$, and in the first hour after barotrauma simulation - $542.1 \pm 4.3 \mu\text{m}$. The average thickness of the wall of the small intestine increased by 0.72 %. On the seventh day, the thickness of the mucous membrane of the small intestine was $541.1 \pm 5.5 \mu\text{m}$, the average value of the parameter of the thickness of the mucous membrane increased by 0.54 %. On the fourteenth day, the average thickness of the mucous membrane of the small intestine was $540.3 \pm 3.3 \mu\text{m}$, therefore, the indicator we studied increased by 0.37 % relative to the similar parameter of the control group. Thus, on the seventh day of the experiment, the average thickness of the mucous membrane of the small intestine relative to the first hour after barotrauma decreased by 0.18 %, and on the 14th day by 0.35 %.

The average value of the *thickness of the muscular layer of the small intestine* of the control group was $147.6 \pm 3.6 \mu\text{m}$, in the first hour after barotrauma simulation it was $151.3 \pm 5.5 \mu\text{m}$, so the average value of the thickness of the muscular layer increased by 2.53 %. On the seventh day, the studied indicator of the thickness of the muscular layer of the small intestine was $150.6 \pm 4.3 \mu\text{m}$ - therefore, the average thickness of the muscular layer increased by 2.02 %. On the fourteenth day, the average value of the thickness of the muscular membrane of the small intestine was $150.6 \pm 3.6 \mu\text{m}$, an increase of the studied parameter compared to the similar indicator of the control group by 2.03 % was established. Thus, on the seventh day of the experiment, the average thickness of the muscular layer of the small intestine relative to the first hour after barotrauma decreased by 0.50 %, on the 14th day by 0.49 %.

The average value of the *small intestine serous membrane thickness* of the control group was $5.351 \pm 0.650 \mu\text{m}$, in the first hour after barotrauma simulation, this value was $8.032 \pm 0.541 \mu\text{m}$, therefore, the average value of the thickness of the serous membrane increased by 50.09 %. On the seventh day, the average thickness of the serous membrane of the small intestine was $7.850 \pm 0.441 \mu\text{m}$. Therefore, the average thickness of the serous membrane increased by 46.73 %. On the fourteenth day, the average value of the thickness of the serous membrane of the small intestine was $5.852 \pm 0.651 \mu\text{m}$, so the studied indicator increased compared to the similar indicator of the control group by 9.35 %. Thus, on the seventh day, the average value of the thickness of the serous membrane of the small intestine relative to the first hour after barotrauma decreased by 2.24 %, and on the 14th day by 27.15 %.

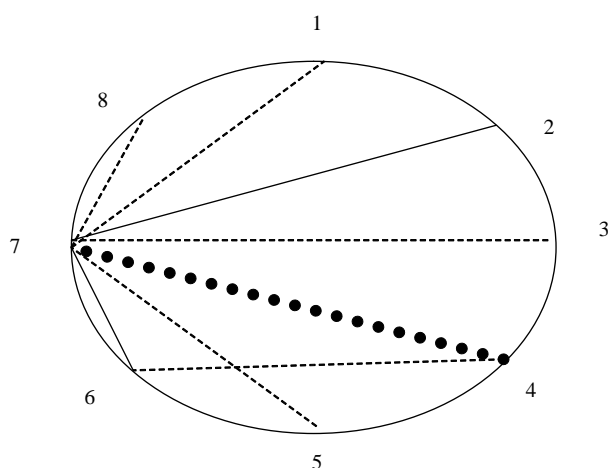


Fig. 1. Correlation relationships between morphometric indicators of the wall of the small intestine 1 - length of villi; 2 - width of villi; 3 - crypt length; 4 - crypt width; 5 - thickness of the intestinal wall; 6 - thickness of the mucous membrane; 7 - thickness of the muscular membrane; 8 - the thickness of the serous membrane; — - correlation is strong; - - - - correlation of average strength; ... - correlation is weak.

After obtaining the morphometric indicators, correlation relationships between them were established (Fig. 1).

Different correlation relationships between the obtained indicators were established. Thus, the average value of the villi length indicator had a strong positive relationship between all parameters, except for the average thickness of the muscle membrane. Similar relationships were observed with the width of the villi. It should be noted that the indicator of the average length of the crypts had strong correlations with all indicators, except for the muscle membrane. The indicator of the average value of the width of the crypts had a strong correlation relationship between all indicators, except for the average value of the indicator of the thickness of the muscular membrane and the thickness of the mucous membrane. The average thickness of the muscle membrane had medium correlations with almost all indicators, except for the average width of the crypts, with which a small weak relationship was established, while a strong relationship was established with the parameter of the average thickness of the mucosal membrane.

Thus, morphometrically, it was established that the muscular membrane is subject to more pronounced changes during barotrauma, and this was confirmed by correlation analysis. The main changes in the intestines under the condition of the impact of the shock wave occur in the muscular membrane.

Discussion

To understand the pathogenesis of the changes that occur after the passage of the front of the shock blast wave, attention should be paid to the peculiarities of the structure of the intestines. The relative mobility in the abdominal

cavity, the volume of the organ and the surface area, the nature of the content in the lumen of the intestines, the peculiarities of angioarchitectonics - all this determines the low threshold of resistance to the effects of barotrauma. This is evidenced by the small but proven number of primary ruptures of the intestinal wall [4, 13]. The intestinal wall has its "weak" places, namely the submucosal layer, where the submucosal microcirculatory vascular plexus is located, the place where the mesentery is attached.

Many authors [11, 20], as well as our study, testify to the heterogeneity not only of the intestinal wall, but also of some areas within one section of the small intestine. During histological, cytometric and ultramicroscopic studies, discrepancies in indicators were established, which indicates a deeper damage to the wall of the small intestine at the cellular level. Violation of hemodynamics at the level of the microcirculatory channel was accompanied by a complex of cellular and tissue changes with the development of various degrees of inflammatory reaction, which had a widespread character. Hemodynamic disturbances and the development of an inflammatory reaction had all the typical signs and depended on the term of the post-traumatic period. In the acute period, at the first stage, against the background of alterative changes, acute hemodynamic disturbances occurred in the form of vasodilatation of arterial vessels, venular and capillary stasis. Hemodynamic disturbances were accompanied by the growth of the edematous component in the intestinal wall, which in turn worsened the permeability of the microvascular channel. In the future, the stage of inflammation unfolds. The degree of infiltration by inflammatory cells (leukocytes, macrophages, etc.) is a marker of the reactivity of the intestinal wall to injury. The chronology of the appearance and disappearance of inflammatory cells is a direct indication of the activity of the reparative process and the antiquity of the traumatic process.

Therefore, the actual direction of morphological experimental studies is the detection of the spectrum of changes in intestinal structures in case of explosive injury. The changes we observed in the small intestine after the impact of shock waves explain the changes that occur clinically during explosions, both in the early stages and in the late period.

The functional activity of the intestinal villi is related to the capture of useful substances after their physical and chemical processing by pancreatic juice, gastric juice and bile. In the intestinal crypts, the processes of proliferation, differentiation and migration of cells are actively taking place. In crypts, as unique biological systems, along with enterocytes, there are goblet cells that participate in the production of intestinal mucus, Paneth cells with acidophilic secretory granules, undifferentiated and endocrine cells [10].

In the future, it is planned to study the morphological and morphometric changes of the intestinal wall at the

ultrastructural level in the dynamics of the post-traumatic period.

Conclusion

1. Thickening of the intestinal wall layers occurred due to intercellular swelling and swelling of stromal elements.
2. The analysis of the morphometric parameters of the wall of the small intestine showed that in experimental rats after barotrauma simulation, quantitative changes occur both at the cellular and tissue levels, which correlate with the observation period.

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КОРЕЛЯЦІЙНІ ВЗАЄМОВІДНОСИНИ ПАРАМЕТРІВ КИШЕЧНОЇ СТІНКИ ПІСЛЯ УДАРНО-ХВИЛЬОВОГО ВПЛИВУ

Кошарний В. В., Абдул-Огли Л. В., Козлов С. В., Рутгайзер В. Г., Рутгайзер О. А.

Вибухи - це фізичні явища, котрі призводять до раптового викиду енергії; вони можуть бути хімічними, ядерними чи механічними. Внаслідок вибуху майже миттєво підвищується тиск, що вищий за атмосферний. Ушкодження органів черевної порожнини після дії факторів вибуху (ударна вибухова хвиля, вражаючі елементи вибухового пристрою, вторинні снаряди, хімічні та термічні фактори) - це достатньо розповсюджена клінічна ситуація. Найбільш вразливими при дії ударної вибухової хвилі серед органів черевної порожнини є тонкий та товстий кишечник. Метою дослідження було вивчення

віддалених наслідків впливу баротравми на морфометричні показники кишечника білих щурів та їх кореляційні взаємозв'язки. Дослідження виконані на 20 білих безпородних статевозрілих щурах вагою 180-200 г. Забарвлення стінки тонкого кишечника проводили гематоксиліном та еозином за загальноприйнятою методикою. Визначали товщину всієї кишкової стінки, слизової, м'язової та серозної оболонок, довжину та ширину ворсинок, глибину та ширину крипт. Статистичну обробку результатів морфометрії проводили за допомогою програми Statistica 10.0. Аналіз гістопатологічних змін в стінці тонкого кишківника шляхом світлової мікроскопії на сьому добу після впливу ударної повітряної хвилі на передню черевну стінку показав достовірне потовщення слизової, підслизової та м'язової оболонок порівняно з контрольною групою тварин. Потовщення шарів стінки кишечника відбувалося за рахунок міжклітинного набряку й набряку стромальних елементів. Впродовж всіх термінів експерименту в слизовій, підслизовій та м'язовій оболонках у всіх досліджуваних препаратах наявною була запальна реакція з переважно нейтрофільною інфільтрацією. В судинах різного діаметра, що належать до слизової та підслизової оболонок виявлено повнокров'я та стази. Аналіз морфометричних показників стінки тонкого кишечника показав, що у піддослідних щурів після моделювання баротравми відбуваються кількісні зміни як на клітинному, так і тканинному рівнях, котрі корелюють з термінами спостереження. М'язова оболонка підлягає більш вираженим змінам при дії ударної хвилі, що підтверджено морфометричними дослідженнями та кореляційним аналізом. Зміни середньої товщини м'язового шару мали середній зв'язок з усіма показниками, окрім ширини крипт та товщини слизової оболонки.

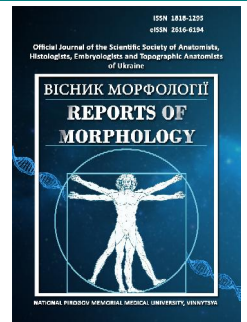
Ключові слова: травна трубка, морфологія, баротравма, стінка кишечника, морфометрія, кореляційний аналіз.



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Morphological changes in the liver of rats after administration of chlorpromazine, depending on the dose and duration of administration

Bailo O. V.¹, Rykalo N. A.²

¹National Pirogov Memorial Medical University, Vinnytsia, Ukraine

²Innsbruck Medical University, Innsbruck, Austria

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CORRESPONDING AUTHOR

e-mail: bayloov@gmail.com

Bailo O. V.

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Chlorpromazine (CPZ) remains a widely used drug in psychiatric practice today. The drug has a hepatotoxic effect, but the possible mechanisms of this side effect have not yet been fully elucidated. The aim of the study was to determine morphological changes in rat liver tissue under chronic toxic effects of chlorpromazine, depending on the dose and duration of its administration. The study was conducted on 60 sexually mature male rats. CPZ was administered intragastrically at different doses (3.5, 7.0, 14.0 and 21.0 mg/kg) for 30 and 60 days. The material was fixed in a 10 % solution of neutral formalin (pH 7.2-7.4) for 24-48 hours, then passed through alcohols of increasing concentration and embedded in paraffin. Serial sections (6-7 μm thick) were prepared from the paraffin blocks and stained with hematoxylin-eosin and picrofuchsin by Van Gieson to determine the degree of fibrotic changes in liver tissue, as well as with Giemsa III to detect fatty degeneration of hepatocytes. The microscopic structure of the hepatic parenchyma was studied using an OLIMPUS BX41 light microscope at 100, 200 and 400x magnification. Morphometric parameters of structural changes were determined using an ocular grid and Image Tulsa 3.6 software. The data were statistically processed by descriptive statistics using the Microsoft Office Excel 2010 spreadsheet processor. When CPZ was administered in different doses and duration, pathological changes of varying severity developed in the liver tissue of rats. In the liver tissue, signs of intracellular and intra-tubular cholestasis are found mainly in the central lobes, accompanied by focal desquamation and proliferation of the biliary epithelium, formation of small-focal, less frequently zonal necrosis of hepatocytes, inflammatory infiltration of portal tracts with its spread to the interlobular stroma and parenchyma. Mitotically active binucleated hepatocytes are the key to the reparative process. Periductal fibrosis develops in the portal sections, marginal proliferation of the bile ducts, hepatocytes with signs of granular and/or fatty dystrophy are noted. In the central veins and vessels of the portal areas, moderate initial sclerotic changes were found, signs of their capillarisation in sinusoids, and the endothelium of the vessels had focal destructive changes. In all portal zones, proliferation of bile ducts and formation of bile pseudo-ducts were observed. Thus, the analysis of the morphometric study data showed that within 60 days of CPZ administration there is a significant increase in the relative volume of connective tissue and stromal-parenchymal index due to a significant decrease in the volume of hepatocytes.

Keywords: chlorpromazine, liver, rats, histological structure, cholestasis, fibrosis.

Introduction

Nowadays, mental illness is quite common and causes a violation of the quality of life of a significant part of the working population. According to the National Institutes of Health (NIH) in 2019, more than 20% of the adult population has mental disorders, and in most cases, patients with

mental disorders require lifelong use of various drugs with potentially hepatotoxic effects. Chlorpromazine (CPZ) remains one of the most commonly used drugs prescribed for the treatment of psychiatric diseases [11]. The issue of CPZ toxicity remains relevant in the 21st century [2, 4, 5,

14]. Thus, in the scientific literature of the last decade, there are many publications that confirm the fact of the toxic effect of CPZ on the liver. In particular, significant changes in biochemical markers (ALT, GGT, ALP) and oxidative stress indicators (catalase, glutathione peroxidase) have been recorded, indicating impaired liver function in patients treated with this drug [3, 12, 21].

CPZ has a rather pronounced side effect on various organs and systems [11]. Scientists have established that as a result of systematic use of CPZ by patients, metabolism and liver function are often disturbed in the human body [4, 14]. CPZ is a derivative of phenothiazine; its metabolism and biotransformation occurs in the liver by sulfoxidation, dimethylation, formation of N-oxide, hydroxylation, with the formation of a sulfoxide metabolite, which causes its high hepatotoxicity. CPZ, a member of the largest class of first-generation antipsychotic agents, is known to cause hepatotoxicity in the form of cholestasis and hepatocellular necrosis in some patients [9]. The mechanism of CPZ hepatotoxicity is unclear, but is thought to result from reactive metabolite formation. Results suggest activation of CPZ to reactive metabolites by 2 pathways in hepatocytes: a cytochrome P450s-catalyzed quinoneimine pathway, and a peroxidase-catalyzed oxidation of CPZ to CPZ radicals [11].

In an experiment on a model of drug-induced cholestasis (DIC) in mice, the mechanisms of development and progression of liver hepatocyte damage under CPZ exposure were investigated. Studies have shown the multifactorial nature of cholestasis in response to the administration of CPZ and other cholestasis-inducing drugs, according to experimental and clinical data. The mechanisms of toxicity include, in particular, the accumulation of biologically active substances, toxic bile metabolites, activation of Ito cells, Kupffer cells [19] and other cells [8].

The aim of the work was to establish morphological changes in the liver tissue of rats under the condition of chronic toxic effects of chlorpromazine depending on the dose and duration of its administration.

Materials and methods

The study was conducted on 60 sexually mature female rats. All experiments were conducted in accordance with the "General Ethical Principles for Animal Experiments" approved by the First National Congress on Bioethics (Kyiv, 2001) and harmonized with the provisions of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Purposes" (Strasbourg, 1986). The bioethics committee of the National Pirogov Memorial Medical University, Vinnytsia approved that the work was performed in compliance with ethical principles (protocol No. 8 dated 22.10.2020).

Before the experiment, the animals were quarantined in a vivarium for 14 days. In general, all animals were evenly divided and 30 rats were assigned to 2 parts of the

experiment by random sampling, taking into account age and initial body weight. The first experimental group included four experimental subgroups (the groups 1.1 - 1.4) and one control (the group 1.0) with an average initial body weight of 128.19 ± 17.41 g; they were involved in a 30-day experiment. The second experimental group also included four experimental subgroups (the groups 2.1 - 2.4) and one control (the group 2.0) with an average initial body weight of 125.0 ± 18.75 g, which was involved in a 60-day experiment. The drug CPZ (trade name "Aminazin", in the dose 25 mg/ml) manufactured by "Galichpharm" (Arterium, Ukraine) was used for the study. CPZ was administered intragastrically with a metal probe with oil once daily during 30 days in doses of 3.5 mg/kg (the group 1.1), 7 mg/kg (the group 1.2), 14 mg/kg (the group 1.3), and 21 mg/kg (the group 1.4) and during 60 days in doses of 3.5 mg/kg (the group 2.1), 7 mg/kg (the group 2.2), 14 mg/kg (the group 2.3), and 21 mg/kg (the group 2.4). The control groups (1.0 and 2.0) included intact animals. The calculation of CPZ doses was performed using the biological activity constant, according to the recommendations of Rybolovlev Yu. R. and Rybolovlev R. S. published in 1979 [15].

All rats were euthanized by intraperitoneal injection of Thiopental solution at the rate of 0.1 mg/g, followed by decapitation. At the very end of each part of the experiment, liver tissue were taken from all rats for morphological and morphometric study. Three liver tissue were taken in each subgroup. Pieces of 1 x 1 cm were cut from the liver tissue.

The material was fixed in a 10 % solution of neutral formalin (pH 7.2-7.4) for 24-48 hours, then it was passed through alcohols of increasing concentration and embedded in paraffin. Serial sections of 6-7 μ m thickness were prepared from the obtained paraffin blocks, which were stained with hematoxylin-eosin, picrofuchsin by the Van Gieson method to determine the degree of fibrous changes in liver tissue, and with Giemsa III to detect fatty degeneration of hepatocytes. The microscopic structure of the hepatic parenchyma was studied using an OLIMPUS BX41 light microscope at 100, 200 and 400 times magnification. The morphometric parameters of structural changes were determined using an ocular grid containing 49 squares, the area of each square is 3.45×10^{-4} mm² at a magnification of 100 and 200 using the Image Tulsa 3.6 program.

The statistical processing of the data was carried out by descriptive statistics using the Microsoft Office Excel 2010 spreadsheet processor. For quantitative indicators, the sample mean, standard deviation, and error of the mean were calculated. In case of normal distribution of quantitative indicators, the Student's t-test was used to compare them. Differences between the analyzed indicators were considered statistically significant at a significance level of 0.05 (5 % error probability, $p < 0.05$).

To comprehensively take into account the pathological changes detected in the liver tissue, the following signs

were determined some parameters: organ structure, preservation and pathological changes of tissue, condition of hepatic beams; condition of portal tracts (width, presence of sclerosis, inflammatory cell infiltration, condition of the terminal lamina, its preservation and degree of disruption, presence of periportal necrosis); interlobular ducts (the presence of proliferation, destruction); condition of vessels (presence of thrombosis, endothelial condition); presence of foci of fibrosis and sclerosis (e.g., septa formation, formation of pseudolobes in the development of cirrhosis, foci of necrosis, indicating their localization and characteristics); condition of sinusoids, condition of stellate reticuloendothelial cells; the state of hepatocytes with the definition of the type of dystrophy, the presence and composition of inflammatory cell infiltration; the presence of cholestasis: intracellular and extracellular, the presence of bile clots, the presence of pericellular, sinusoidal, intrahepatic fibrosis.

Results

In experimental group 1.1, macroscopically, the liver was moderately enlarged in size, with a smooth surface, fine-grained, pale brown in color with a yellowish-greenish tint, with full blood vessels.

Morphological changes of the liver in rats of experimental group 1.1 (with the introduction of CPZ in a dose of 3.5 mg/kg). The features of the histological structure of the liver were full blooded sinusoidal capillaries, central veins, portal veins with dilated lumens, moderate edema of the vascular walls and flattening of the endothelium. Parenchyma with indistinct division into lobules. Most of the hepatic beams with signs of discomplete. Mostly all hepatocytes were polygonal in shape with clear contours, had a round basophilic nucleus and moderately eosinophilic cytoplasm, sometimes with eosinophilic granular inclusions (signs of granular dystrophy). In the cytoplasm of some hepatocytes, acidophilic bodies, areas of destruction and homogenization of liver cells were detected. In some observations, some liver cells showed signs of small- and large-droplet obesity. Single binucleated hepatocytes were detected as a manifestation of regeneration (1-2 cells in the field of view x100). Along with these changes, dilation, edema, and distention of the portal tracts were detected. Fibrous changes in the liver parenchyma were not detected (Fig. 1, 2).

The relative volume of hepatocytes was 72.30 ± 2.08 %. The relative volume of connective tissue was 4.511 ± 0.741 %, vessels - 23.20 ± 1.03 %, stromal-parenchymal index - 0.381 ± 0.004 . Morphometrically, the relative volume of the bile ducts and tubules was 9.031 ± 1.081 %.

Morphological changes of the liver in rats of experimental group 1.2 (CPZ in a dose of 7 mg/kg). The histological examination of the liver tissue of rats showed hemorrhage of central veins, sinusoidal capillaries, portal veins with moderate edema of the vascular walls, dystrophic changes and flattening of the endothelium. The initial phenomena

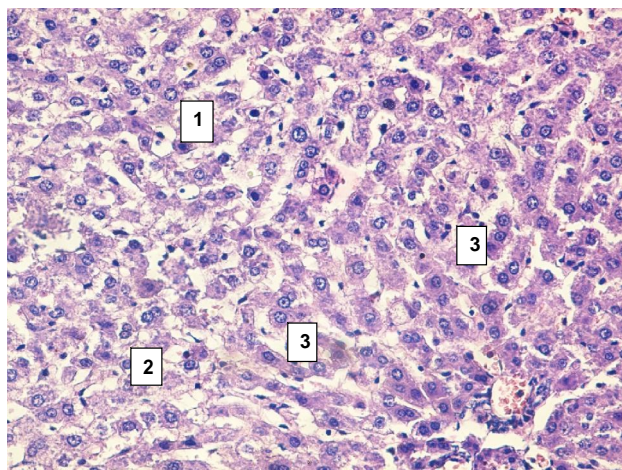


Fig. 1. Liver tissue of rat of group 1.1. 1 - pronounced granular and focal small-vacuolar dystrophy of hepatocytes with initial lysis and partial necrosis; 2 - discomplete hepatic beams; 3 - binucleated hepatic cells. Hematoxylin-eosin stain. x200.

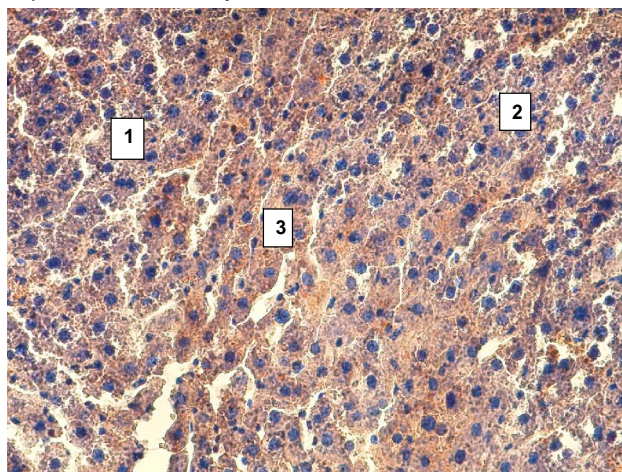


Fig. 2. Liver tissue of rat of group 1.1. 1 - pronounced granular and focal small-vacuolar dystrophy of hepatocytes with initial lysis and partial necrosis; 2 - discomplete hepatic beams; 3 - binucleated hepatic cells. Sudan III staining. x200.

of centrilobular cholestasis were determined, in which the blockade of stellate reticuloendothelial cells by bile pigments was observed. Most hepatocytes were in a state of granular and fatty dystrophy. Some hepatocytes were in a state of necrosis. In the cytoplasm of most hepatocytes, acidophilic bodies, areas of destruction and homogenization of liver cells were determined. Two-nucleated hepatocytes (3-4 cells in the field of view ?100) were detected as a sign of regenerative processes.

Morphometrically, the relative volume of hepatocytes was 72.61 ± 2.63 %, connective tissue was 4.911 ± 1.121 %, blood vessels - 22.51 ± 1.58 %, stromal-parenchymal index - 0.371 ± 0.003 . In some cases, a small inflammatory cell infiltrate was detected, consisting of mononuclear cells, histiocytes, and single segmented leukocytes. Morphometrically, the relative volume of the bile ducts and tubules was 9.211 ± 1.111 %.

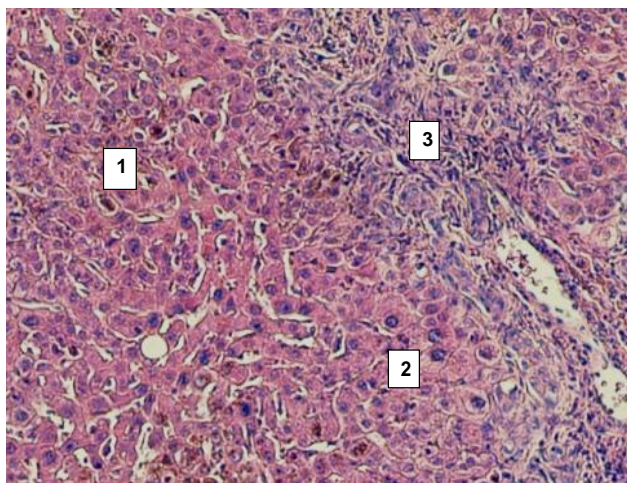


Fig. 3. Liver tissue of rat 1.2 group. 1 - bile imbibition of many hepatocytes and stellate reticuloendothelial cells; 2 - significant granular dystrophy of hepatocytes, moderate nuclear polymorphism, initial lysis of individual hepatocytes; 3 - inflammatory cell infiltrate of mononuclear cells, histiocytes. Hematoxylin and eosin staining. x200.

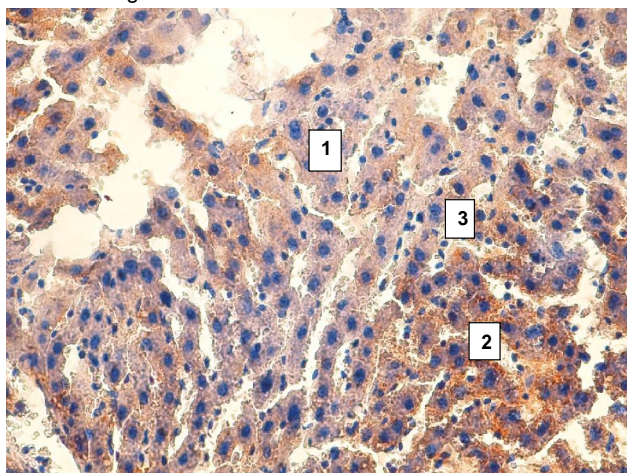


Fig. 4. Liver tissue of rat 1.2 group. 1 - single binucleated hepatocytes; 2 - fatty degeneration of hepatocytes, moderate nuclear polymorphism, initial lysis of individual hepatocytes; 3 - slight inflammatory cell infiltration of mononuclear cells, histiocytes. Sudan III staining. x200.

There was also a slight dilation, edema and distention of the portal tracts (Fig. 3, 4).

Morphological changes of the liver in rats of experimental group 1.3 (CPZ in a dose of 14 mg/kg). Histologically, the liver biopsies showed even more pronounced centrilobular cholestasis compared to previous studies, in which blockade of stellate reticuloendothelial cells by bile pigments was observed. Most hepatocytes were in a state of necrosis. Peripherally, single binuclear hepatocytes were detected as a manifestation of repair processes (3-4 in the field of view x100). Acidophilic bodies were also detected in the cytoplasm of some hepatocytes, and there were areas of destruction and homogenization of hepatic cells with the formation of so-called pseudoglandular structures around

bile thrombi. The liver stroma was represented by loose fibrous tissue with intense fuchsinophilia in the portal tracts and walls of large vessels.

Morphometrically, the relative volume of hepatocytes was 73.31 ± 2.54 %, connective tissue was 5.111 ± 1.141 %, vessels - 21.61 ± 1.59 %, stromal-parenchymal index - 0.361 ± 0.002 . In some cases, there was a mild inflammatory cell infiltrate consisting of mononuclear cells, histiocytes, segmented leukocytes. Morphometrically, the relative volume of the bile ducts and tubules was 8.611 ± 1.031 %.

Dilation, edema and distention of the portal tracts were also detected. There was a proliferation of delicate fibrous tissue around the vessels (Fig. 5).

Morphological changes of the liver in rats of experimental group 1.4 (CPZ in a dose of 21 mg/kg). At the histological examination of this group rat liver tissue slices the morphological features were characterized by a deeper progression of intraluminal and portal pathological changes. Groups of hepatic cells were subject to necrosis and lysis, focal biliary infarcts were formed, around which reactive inflammation developed in the form of accumulations of segmented leukocytes and macrophages.

There was a slight collapse of the stroma due to small foci of fibrosis with moderate infiltration of lymphohistiocytic elements and focal necrosis. Morphometrically, the relative volume of hepatocytes was 69.81 ± 2.24 %, connective tissue was 6.911 ± 1.321 %, vessels - 23.31 ± 1.61 %, stromal-parenchymal index - 0.421 ± 0.006 (Table 1). The lumens of some bile ducts were dilated, contained thickened bile, sometimes with the formation of bile cylinders.

Morphometrically, the relative volume of the bile ducts and tubules was 7.611 ± 1.051 %. The largest number of biliary cylinders was determined in the center of the lobules,

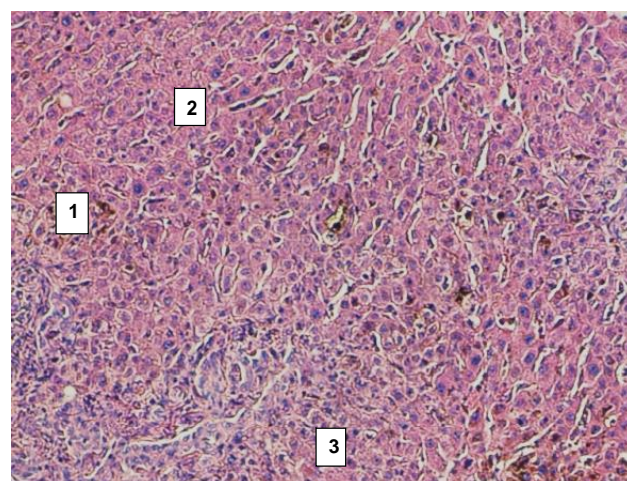
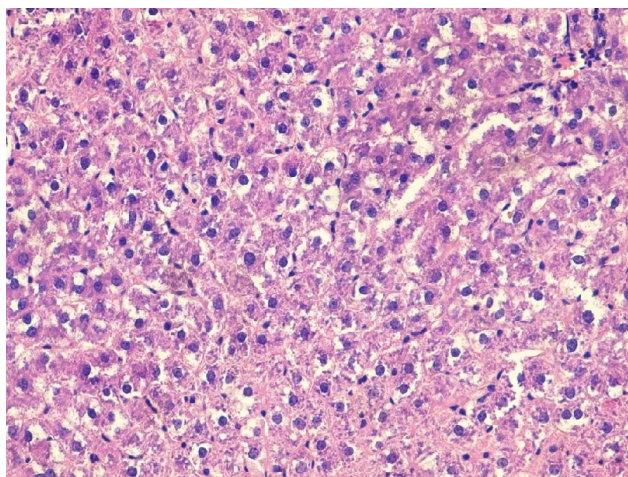
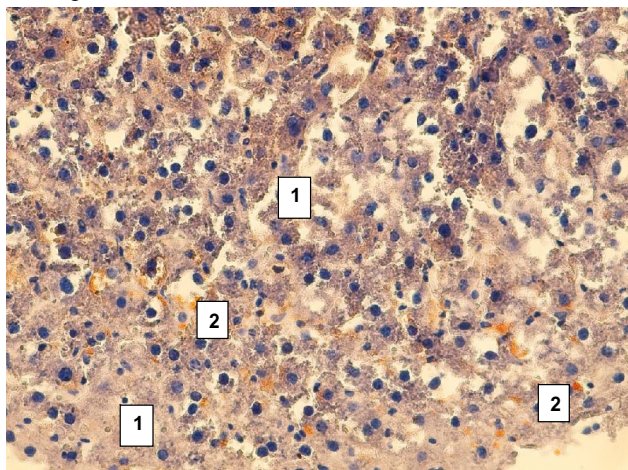


Fig. 5. Rat liver tissue (experimental group 1.3). 1 - bile imbibition of many hepatocytes and stellate reticuloendothelial cells with formation of bile thrombi; 2 - moderate granular dystrophy of hepatocytes, significant nuclear polymorphism, lysis of individual hepatocytes; 3 - focal lymphohistiocytic infiltration. Hematoxylin and eosin staining. x200.

Table 1. Relative volumes of structural components of the liver (M±m) of rats of the first research group.

Structural components	Group 1.1	Group 1.2	Group 1.3	Group 1.4
Hepatocytes, %	72.31±2.08	72.61±2.63	73.31±2.54	69.81±2.24
Bile ducts, %	9.031±1.081	9.211±1.111	8.611±1.031	7.611±1.051
Connective tissue, %	4.511±0.741	4.911±1.121	5.111±1.141	6.911±1.321
Vessels, %	23.21±1.03	22.51±1.58	21.61±1.59	23.31±1.61
Stromal-parenchymal index	0.381±0.004	0.371±0.003	0.361±0.002	0.421±0.006

in hepatic cells, and less often in the cytoplasm of stellate reticuloendothelial cells. Bile droplets and grains were detected in the cytoplasm. Sometimes bile stained the entire cytoplasm of cells. As a result of cytotoxic action,

**Fig. 6.** Rat liver tissue (1.4 subgroup). Pronounced granular and vacuolar dystrophy of hepatocytes, significant nuclear polymorphism, lysis of hepatocyte groups. Hematoxylin and eosin staining. x200.**Fig. 7.** Rat liver tissue (1.4 subgroup). 1 - pronounced hepatic beam discomplexity, dystrophic polymorphism of hepatocytes; 2 - fatty degeneration of hepatocytes, dystrophic polymorphism of hepatocytes. Staining with Sudan III. x200.

degeneration, degeneration, lysis of hepatocytes with their subsequent necrosis occurred. Two-nucleated hepatocytes were detected in the amount of 6-8 cells in the field of view x100 (Fig. 6, 7).

Morphological changes of the liver in the rats of the second research group after the administration of CPZ for 60 days. In rats of the second experimental group, the liver was also enlarged in size, compacted, the tissue was yellow-green in color, the vessels were full of blood. In all cases of cirrhosis development, the liver was macroscopically reduced in size, with a fine crumbly surface, dense consistency. On section, the liver tissue was yellowish-gray in color, low in blood, represented by multiple nodules separated from each other by gray layers.

Morphological changes of the liver in rats of experimental group 2.1 (CPZ in a dose of 3.5 mg/kg). Morphological changes in the liver of rats were characterized by the deeper pathomorphological changes, which consisted in further progression of intra-lobar and portal disorders. Dystrophic and degenerative changes significantly prevailed over the manifestations of intracellular hepatocyte regeneration, which negatively affected the state of the extracellular matrix and contributed to the formation of fibrous connective tissue septa with further development of cirrhosis.

As a response to the cytotoxic effect of bile components, desquamation of the bile duct epithelium with partial proliferation was observed. Deeper alternative changes in hepatocytes were detected. Most hepatocytes were in a state of granular and fatty dystrophy. Some hepatocytes were in a state of necrosis. In the cytoplasm of most hepatocytes, acidophilic bodies, areas of destruction and homogenization of liver cells were detected. Binuclear hepatocytes were detected in the amount of 5-7 cells in the field of view x100.

Morphometrically, the relative volume of the bile ducts and tubules was 11.21±1.12 %. The relative volume of hepatocytes tended to decrease further and amounted to 66.81±2.04 % (Table 2).

In the portal tracts, a focal inflammatory reaction was determined, which was a response to cholestasis. Morphometrically, the relative volume of connective tissue was 6.211±1.361 %, vessels - 16.81±1.84 %, stromal-

Table 2. Relative volumes of structural components of the liver (M±m) of rats of the second research group.

Structural components	Group 2.1	Group 2.2	Group 2.3	Group 2.4
Hepatocytes, %	66.81±2.04	62.41±2.01	58.21±1.42	47.31±1.23
Bile ducts, %	11.21±1.12	15.21±1.12	18.41±1.16	22.31±1.19
Connective tissue, %	6.210±1.360	7.911±1.381	12.61±1.64	18.56±1.68
Vessels, %	16.81±1.84	14.61±1.63	12.11±1.23	10.12±1.27
Stromal-parenchymal index	0.511±0.080	0.611±0.090	0.721±0.011	1.121±0.151

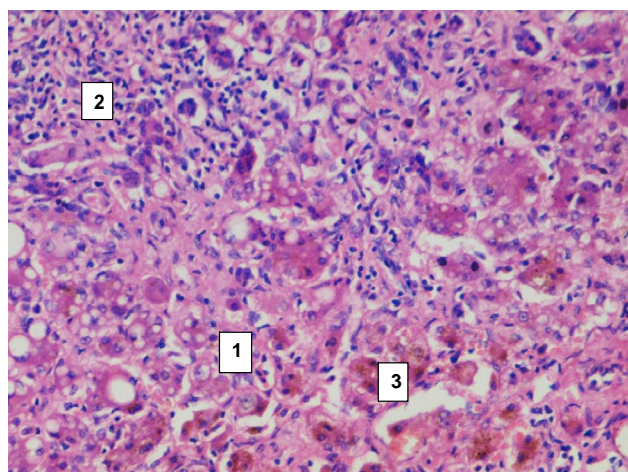


Fig. 8. Rat liver tissue (experimental subgroup 2.1). 1 - hepatic beam discomplexity, pronounced dystrophic polymorphism of hepatocytes; 2 - fibrosis of portal tract stroma with infiltration of its lymphocytes; 3 - hepatocytes with signs of cholestasis. Hematoxylin and eosin staining. x200.

parenchymal index - 0.511 ± 0.081 (Fig. 8).

Morphological changes of the liver in rats of experimental group 2.2 (CPZ in a dose of 7 mg/kg). Liver tissue showed a pronounced granular and small-vacuolar fatty degeneration of hepatocytes. Also, some animals had fatty liver hepatitis. Small fatty drops were detected in the cytoplasm of hepatocytes located mainly in the center of the liver lobes (centrilobular). There was a pronounced discomposition of the hepatic beams, widespread foci of hepatic tissue collapse with significant narrowing of the sinusoidal spaces, with a complete absence of regenerative processes in the liver parenchyma. Along with dystrophic changes in hepatocytes of varying severity,

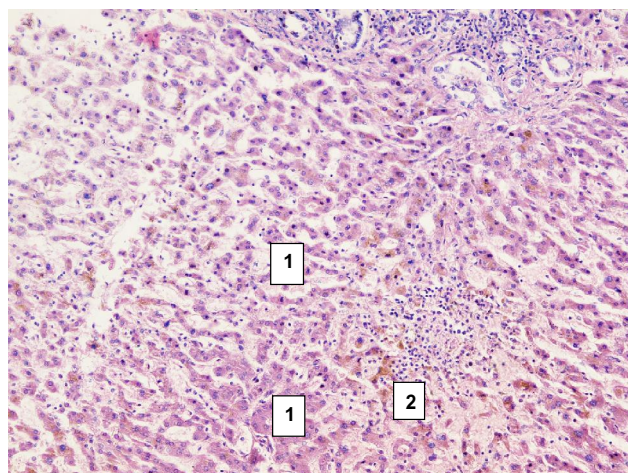


Fig. 9. Rat liver tissue (experimental group 2.2). 1 - heteromorphism of hepatocytes, polymorphism and polychromy of nuclei, in many cells - the initial phenomena of apoptosis in the form of pyknosis, compaction of the nucleus, protein dystrophy of a significant part of hepatocytes, complete disruption of the beam structure of hepatocytes; 2 - intracellular cholestasis with perifocal lymphohistiocytic infiltration. Hematoxylin and eosin staining. x100.

proliferation, accumulation and activation of macrophages, which are designed to capture and destroy damaged and dead liver structures during the disease, were observed.

In some observations, a combination of hydropic and fatty dystrophy was detected. The latter was small-droplet and focal in nature. Heteromorphism of hepatocytes, polymorphism and polychromy of nuclei were observed, and in some cells - the initial phenomena of apoptosis in the form of pyknosis, compaction and deformation of the nucleus.

The cells of the inflammatory infiltrate were represented by lymphocytes, which were detected both in the portal tracts and in the sinusoids in the form of chains of lymphocytes. There was also infiltration with segmented leukocytes and macrophages, among which a large number of bile-containing macrophages were detected. Small hemorrhages were noted against the background of lymphohistiocytic infiltration of the portal tracts. In the portal tracts, a focal inflammatory reaction was determined, which was a response to cholestasis. Binuclear hepatocytes were determined in the amount of 6-8 cells in the field of view x100 (Fig. 9).

Morphometrically, the relative volume of the bile ducts and tubules was 15.21 ± 1.12 %; the relative volume of hepatocytes tended to decrease further and amounted to 62.41 ± 2.01 %; the relative volume of connective tissue was 7.911 ± 1.381 %, vessels - 14.61 ± 1.63 %, stromal-
parenchymal index - 0.611 ± 0.091 .

Morphological changes of the liver in rats of experimental group 2.3 (CPZ in a dose of 14 mg/kg). The pathomorphological features in the rat liver slices were signs of further development of the periductal sclerotic process. Bile salts caused further destruction of the bile duct epithelium. At the same time, the permeability of the bile duct walls increased, bile pigments leaked into the surrounding fibrous tissue and blood vessels, which caused inflammation in the portal fields and periductal fibrosis. The formation of fibrous septa in combination with nodular regeneration of the liver parenchyma led to a violation of the liver histoarchitecture with subsequent transformation into cirrhosis.

In cases with severe hepatic tissue remodeling, a pronounced proliferation of perivascular fibrous tissue was detected with subsequent deformation of the vascular lumens. The formation of a system of capillarization of sinusoids of false particles was observed by the appearance of a connective tissue membrane in the sinusoids.

Almost all observations revealed hepatocytes in a state of deep dystrophic changes (close to total vacuolar dystrophy), which were located mainly in the central parts of the liver lobes, in a smaller number - in the peripheral parts. Against the background of severe dystrophic changes in the liver tissue, sclerotic processes of the stroma were determined in varying degrees of severity - from the proliferation of fine fibrous tissue around the central veins

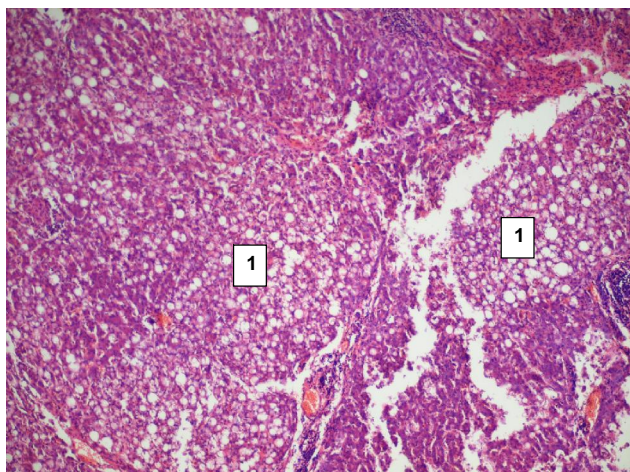


Fig. 10. Rat liver tissue (experimental group 2.3). 1 - total vacuolar dystrophy of hepatocytes with complete decomplexation of hepatic beams. Hematoxylin and eosin staining. x100.

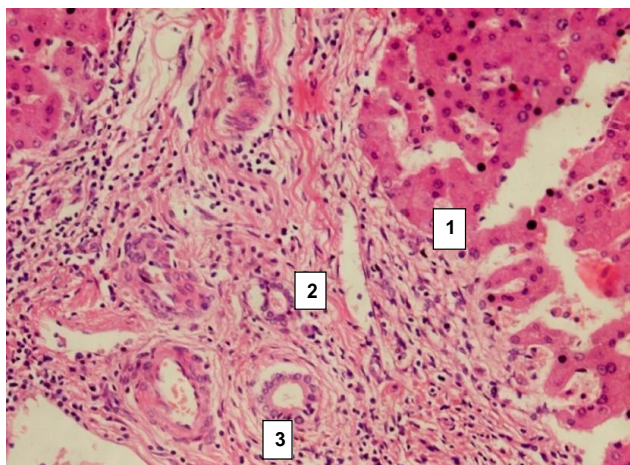


Fig. 11. Rat liver tissue (experimental group 2.2). 1 - pronounced discomposition of hepatic beams, dystrophic polymorphism of hepatocytes in the pseudolobule; 2 - fibrosis of the portal tract stroma with diffuse infiltration of lymphocytes and histiocytes; 3 - proliferation of small bile ducts. Hematoxylin and eosin staining. x200.

with a slight expansion of the portal tracts to severe periportal and centrilobular perivenular fibrosis, as well as pericellular sclerosis in some places. Along with these changes, proliferation of the bile ducts with cholestasis was detected. In fibrous septa and stroma of dilated sclerotic portal tracts, focal inflammatory infiltration was determined mainly from lymphocytes and macrophages with an admixture of neutrophils. Binuclear hepatocytes were detected in the amount of 3-4 cells in the field of view ?100 (Fig. 10, 11).

Morphometrically, the relative volume of the bile ducts and tubules was 18.41 ± 1.16 %; the relative volume of hepatocytes tended to decrease further and amounted to 58.21 ± 1.42 %; the relative volume of connective tissue was 12.61 ± 1.64 %, vessels - 12.11 ± 1.23 %, stromal-parenchymal index tended to further increase and amounted to 0.721 ± 0.111 .

Morphological changes of the liver in rats of experimental group 2.4 (CPZ in a dose of 21 mg/kg). In most of the observations, portal cirrhosis was detected in the liver tissue. There was an insertion of thin fibrous septa into the liver lobes with subsequent connection of the central veins with the vessels of the portal tracts with the formation of small false lobes consisting of proliferating hepatocytes in a state of fatty and protein dystrophy with the absence of radial orientation of the hepatic beams.

The analysis of morphometric data revealed a further increase in the relative volume of connective tissue and stromal-parenchymal index due to a decrease in the relative volume of hepatocytes, as well as an increase in the number of bile ducts due to their proliferation and the formation of bile pseudo-ducts and a decrease in the number of vessels.

There was further deeper destruction of the organ parenchyma with the convergence of neighboring enlarged portal fields, and small groups of hepatocytes (hepatic cell islets) that survived fell into the enlarged portal zones. The binucleated hepatocytes were not detected. Thus, necroinflammatory changes gradually transform into fibrosis and later into cirrhosis. Fibrotic changes are evidence of progression of subhepatic jaundice, they lead to a gross violation of histoarchitectonics and the steady development of cirrhosis. Before the features of the former architectonics are completely destroyed, some areas of the tissue become nodular, while adjacent areas still retain a lobular structure. This condition is regarded as incomplete cirrhosis. In some cases, total liver cirrhosis was determined (Fig. 12).

Morphometrically, the relative volume of the bile ducts and tubules was 24.31 ± 1.19 %; the relative volume of hepatocytes tended to decrease further and amounted to

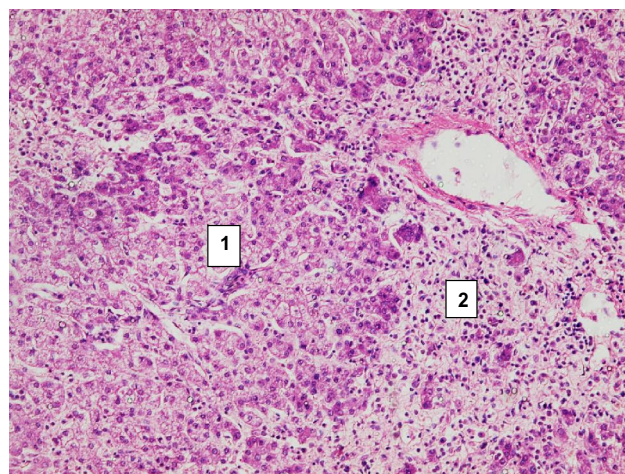


Fig. 12. Rat liver tissue (experimental group 2.4). 1 - pronounced discomplexity of hepatic beams, dystrophic polymorphism of hepatocytes, significant granular and vacuolar dystrophy of hepatocytes; 2 - widespread fibrosis with diffuse infiltration of lymphohistiocytic elements; formation of pseudoparticles. Hematoxylin-eosin stain. x100.

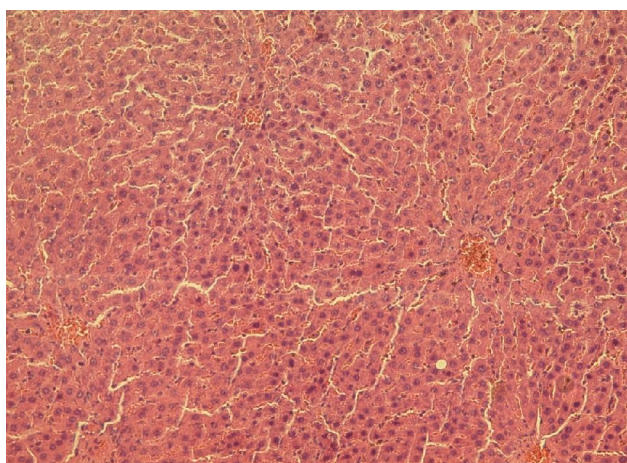


Fig. 13. Liver of normal histological structure - control group. The beam structure of hepatocytes is preserved. There are no dystrophic changes in hepatocytes. Hematoxylin-eosin stain. x100.

47.31±1.23 %; the relative volume of connective tissue was 18.56±1.68 %, vessels - 10.12±1.27 %, stromal-parenchymal index tended to further increase and amounted to 1.121±0.151.

Morphological changes of the liver in rats of the control group. During the histological examination of liver tissue in rats of the control group, in most cases the tissue of the organ had a normal histological structure.

The liver parenchyma consisted of liver lobes that had the shape of high prisms with a flat base and a slightly convex top. In some places, simple particles merged with their bases two or more, forming complex larger particles. Interlobular connective tissue was poorly developed, so the partial structure is poorly expressed. It forms the stroma of the organ, blood vessels and excretory ducts pass through it, morphologically related to the liver lobes. The walls of interlobular capillaries are formed by special endothelial cells called stellate endothelial (Kupffer) cells. They have the ability to absorb substances circulating in the blood, capture and digest cell debris, bacteria, and fat droplets.

Hepatic lobes consisted of liver cells - hepatocytes, arranged in the form of strands - liver plates. Intralobular blood capillaries pass between the liver plates. Hepatic lobes anastomose with each other and form a mesh. Between the liver cells that make up the plate, there are narrow gaps - bile capillaries that do not have their own wall. There is no direct connection between bile and blood capillaries, as they are separated by liver cells. Hepatic plates do not have basement membranes. Inside the liver lobes, connective tissue is almost completely absent, only between the walls of the intralobular capillaries between the liver plates there is a fairly dense network of thin reticular fibers (Fig. 13).

Discussion

The results of our histological examination of the liver tissue of rats treated with CPZ at a dose of 3.5 to 21 mg/kg

for one and two months are in line with the literature. It is known that under the influence of CPZ, markers of early liver fibrosis increased significantly (early fibrosis markers Col1a1 and Hsp47) [8], as cholestasis, according to various researchers, contributes to the early development and progression of liver fibrosis [6, 7, 16, 23]. This is due to the activation of stellate cells due to the hepatotoxicity of Cholinesterase. It is the toxicity of this drug that can explain the development of early fibrosis by the mechanism of cholestasis [20] through participation in the direct and reverse mechanisms of Bsep and Mrp4 gene expression, which is confirmed by various scientists [9, 18].

In an *in vitro* experiment, it was found that perfusion of the choleric liver in rats dramatically reduced bile outflow. This was accompanied by fragmentation and a loss of canalicular microvilli, dilatation of canaliculi, and thickening of pericanalicular ectoplasm. Cholestasis is a typical mechanism in the development of drug damage to the liver, including a rather high risk with the introduction of CPZ [8, 17].

Main changes, such as proliferation of bile duct, expansion of hepatic sinus, necrosis of hepatocyte, and effusion of inflammation factors, were observed in CPZ-stimulated hepatotoxicity animal models [22].

Early hepatic effects of CPZ were investigated using the differentiated human hepatoma HepaRG cells [1]. Among other mechanisms, oxidative stress plays a major role as both a primary causal and an aggravating factor in the early CPZ-induced intrahepatic cholestasis in human hepatocytes.

Also were describe a case of a primary biliary cirrhosis-like syndrome developed after 2 week of CPZ therapy in 33-yr-old pregnant woman. The pathological substrate of this severe and prolonged cholestatic reaction was found to be the vanishing bile duct syndrome with a marked transient pseudoxanthomatosis [11].

Conclusion

1. The data of a comprehensive morphological study showed that when CPZ is administered in different doses, pathological changes of varying severity develop in the liver tissue, depending on the duration of the drug administration. In the liver tissue, there are signs of intracellular and intra-tubular cholestasis mainly in the central lobes, accompanied by focal desquamation and proliferation of the biliary epithelium, formation of small-focal, less often zonal necrosis of hepatocytes, inflammatory infiltration of portal tracts with its spread to the interlobular stroma and parenchyma. Along with inflammatory and destructive processes in the liver, signs of a reparative process are detected: mitotically active binuclear hepatocytes are found near the necrosis foci, mildly expressed, mainly periductal fibrosis develops in the portal areas, and marginal proliferation of the bile ducts is noted.

2. In most of the preserved and newly formed

hepatocytes, signs of granular (protein) and/or fatty dystrophy are detected.

3. In the central veins and vessels of portal zones, there are mild initial sclerotic changes, signs of their capillarization in the sinusoids, and vascular endothelium with focal destructive changes. In some observations, periductal fibrosis with a significant number of fibroblasts, the formation of thin connective tissue septa that invade

the interlobular stroma and parenchyma increases in the portal areas. In all portal zones, proliferation of bile ducts and formation of bile pseudo-ducts are observed.

4. Analysis of the morphometric study data showed that in the 2nd group of the experiment there was a significant increase in the relative volume of connective tissue and stromal-parenchymal index due to a significant decrease in the volume of hepatocytes.

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МОРФОЛОГІЧНІ ЗМІНИ ПЕЧІНКИ ЩУРІВ НА ТЛІ ВВЕДЕННЯ ХЛОРПРОМАЗИНУ, ЗАЛЕЖНО ВІД ДОЗИ ТА ТРИВАЛОСТІ ВВЕДЕННЯ

Байло О.В., Рикало Н.А.

Хлорпромазин (ХПЗ) залишається широко вживаним препаратом у психіатричній практиці сьогодення. Препарат має гепатотоксичний вплив, проте можливі механізми даного побічного ефекту ще остаточно не з'ясовані. Метою роботи було встановити морфологічні зміни в тканині печінки щурів за умови хронічної токсичної дії хлорпромазину залежно від дози та тривалості його введення. Дослідження проведено на 60 статевозрілих щурах-самцях. ХПЗ вводили інтрагастрально у різних дозах (3,5; 7,0; 14,0 та 21,0 мг/кг) впродовж 30 і 60 днів. Матеріал фіксували в 10 % розчині нейтрального формаліну (рН 7,2-7,4) впродовж 24-48 годин, потім проводили через спирти зростаючої концентрації та заливали у парафін. З отриманих парафінових блоків готували серійні зрізи товщиною 6-7 мкм, які забарвлювали гематоксилін-еозином та пікрофуксином за Ван Гізоном для визначення ступеня фіброзних змін у тканині печінки, а також за Гімзою III для виявлення жирової дистрофії гепатоцитів. Мікроскопічну будову печінкової паренхіми вивчали за допомогою світлового мікроскопа OLIMPUS BX41 при 100, 200 і 400-кратному збільшенні. Морфометричні параметри структурних змін визначали за допомогою окулярної сітки та програми Image Tulsa 3.6. Статистичну обробку даних проводили методами описової статистики з використанням табличного процесора Microsoft Office Excel 2010. При введенні ХПЗ у різних дозах і тривалості у тканині печінки щурів розвиваються патологічні зміни різного ступеня виразності. У тканині печінки виявляють ознаки внутрішньоклітинного та внутрішньоканальцевого холестазу переважно в центральних частках, котрі супроводжуються вогнищевою десквамацією та проліферацією жовчного епітелію, утворенням дрібновогнищевих, рідше зональних некрозів гепатоцитів, запальною інфільтрацією портальних трактів з поширенням її на міжчасточкову строму та паренхіму. Ознаками репаративного процесу є міотично активні двоядерні гепатоцити. У портальних відділах розвивається перидуктальний фіброз, відзначається крайова проліферація жовчних проток, гепатоцити з ознаками зернистої та/або жирової дистрофії. У центральних венах і судинах портальних зон встановлені помірні початкові склеротичні зміни, ознаки їх капіляризації в синусоїдах, ендотелій судин був з вогнищевими деструктивними змінами. У всіх портальних зонах спостерігається проліферація жовчних проток і формування жовчних псевдопроток. Таким чином, аналіз даних морфометричного дослідження показав, що впродовж 60 днів введення ХПЗ відбувається достовірне збільшення відносного об'єму сполучної тканини та стромально-паренхіматозного індексу за рахунок достовірного зменшення об'єму гепатоцитів.

Ключові слова: хлорпромазин, печінка, щури, гістологічна структура, холестаз, фіброз.

REQUIREMENTS FOR ARTICLES

For publication, scientific articles are accepted only in English only with translation on Ukrainian, which contain the following necessary elements: UDC code; title of the article (in English and Ukrainian); surname, name and patronymic of the authors (in English and Ukrainian); the official name of the organization (institution) (in English and Ukrainian); city, country (in English and Ukrainian); structured annotations (in English and Ukrainian); keywords (in English and Ukrainian); introduction; purpose; materials and methods of research; research results; discussion; conclusions; bibliographic references.

The title of the article briefly reflects its contents and contains no more than 15 words.

Abstract. The volume of the annotation is 1800-2500 characters without spaces. The text of an annotation in one paragraph should not contain general phrases, display the main content of the article and be structured. The abstract should contain an introductory sentence reflecting the relevance of the study, the purpose of the study, a brief description of the methods of conducting research (2-3 sentences with the mandatory provision of the applied statistical methods), a description of the main results (50-70% of the volume of the abstract) and a concise conclusion (1 sentence). The abstract should be clear without familiarizing the main content of the article. Use the following expressions: "Detected ...", "Installed ...", "Fixed ...", "Impact assessed ...", "Characterized by regularities ...", etc. In an annotation, use an active rather than passive state.

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"Introduction"

The introduction reflects the state of research and the relevance of the problem according to the world scientific literature (at least 15 references to English articles in international journals over the past 5 years). At the end of the entry, the purpose of the article is formulated (contains no more than 2-3 sentences, in which the problem or hypothesis is addressed, which is solved by the author).

"Materials and methods"

The section should allow other researchers to perform similar studies and check the results obtained by the author. If necessary, this section may be divided into subdivisions. Depending on the research objects, the ethical principles of the European Convention for the protection of vertebrate animals must be observed; Helsinki Declaration; informed consent of the surveyed, etc. (for more details, see "Public Ethics and its Conflict"). At the end of this section, a "statistical processing of results" section is required, which specifies the program and methods for processing the results obtained by the automobile.

"Results"

Requirements for writing this section are general, as well as for all international scientific publications. The data is presented clearly, in the form of short descriptions, and must be illustrated by color graphics (no more than 4) or drawings (no more than 8) and tables (no more than 4), the information is not duplicated.

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In the discussion, it is necessary to summarize and analyze the results, as possible, compare them with the data of other researchers. It is necessary to highlight the novelty and possible theoretical or practical significance of the results of the research. You should not repeat the information already listed in the "Introduction" section. At the end of the discussion, a separate paragraph should reflect the prospects for using the results obtained by the author.

"Conclusion"

5-10 sentences that summarize the work done (in the form of paragraphs or solid text).

"Acknowledgements"

Submitted after conclusion before bibliographic references.

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Concluding remarks

The manuscript should be executed in such a way that the number of refinements and revisions during the editorial of the article was minimal.

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e-mail: tvory2009@gmail.com

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