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MORPHOLOGICAL FEATURES OF THE MYOCARDIUM IN HYPERHOMOCYSTHINEMIA ON THE BACKGROUND OF THYROID DISORDERS

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The thyroid gland pathologies occupy one of the leading places among endocrine disorders. Metabolic changes that occur in hyper- or hypothyroidism lead to dysfunction of many organs and systems, first of all, the cardiovascular system. Cardiovascular diseases are one of the most acute medical and social problems of modern society. Currently, it has been established that an increase in homocysteine levels has a significant role in the progression of coronary heart disease and its complications. However, several scientific publications do not sufficiently address the impact of hyperhomocysteinemia on the functional myocardium condition in thyroid pathology, which requires a more detailed study of this problem. The study aimed to establish the reorganization of the structural components of the myocardium under the conditions of experimental hyperhomocysteinemia on the background of hyper- and hypothyroidism. Histological examination of left ventricle pieces of the rat's heart was conducted in the study. Significant microscopic changes of stromal-vascular-parenchymal components were found in the myocardium of laboratory rats with HHCy, hyper-, and hypothyroidism. More pronounced necrotic and degenerative changes of cardiomyocytes have been established in the conditions of combined hyper- and HHCy and hypothyroidism and HHCy action.

Key words: *hyperthyroidism, hypothyroidism, hyperhomocysteinemia, myocardium.*

The connection of the publication with planned research works. The study is a fragment of the National Pirogov Memorial Medical University research topic "Influence of exogenous and endogenous factors on the metabolism of hydrogen sulfide and associated metabolic processes in normal and in pathology", state registration № 0113U006461.

Introduction. Cardiovascular disease (CVD) is recognized as the leading cause of death and permanent disability in the world [1, 2, 3, 4]. Several epidemiological studies have shown that homocysteine (HCy) is an independent risk factor for CVD [5, 6], and hyperhomocysteinemia (HHCy) leads to heart attacks and strokes [2, 7].

Myocardial and vascular endothelial tissues have receptors for thyroid hormones and are sensitive to changes in the concentration of circulating thyroid hormones [8, 9]. It was established that minor changes in the concentration of thyroid hormones, that have been observed in subclinical hyper- or hypothyroidism affect the cardiovascular system negatively [10]. Some of the potential mechanisms linking these two conditions are dyslipidemia, endothelial dysfunction, changes in blood pressure, and the direct effect of thyroid hormones on the myocardium. It has been found that the treatment of thyroid disease improves the cardiovascular system condition, which provides potential benefits to reduce the risk of CVD [11]. Experimental studies have also shown that thyroid hormones may play an important therapeutic role in reducing the heart attack risk and improving myocardial function after an acute myocardial infarction.

The aim of the study was to establish the reorganization of the structural myocardium components under the conditions of experimental HHCy on the background of hyper- and hypothyroidism.

Object and methods of research. The experiments were conducted on 50 outbred white male rats weighing 180-200 g. Rats were kept at standard light day on a usual diet. All studies were conducted in compliance with the requirements of humane treatment of experimental animals, regulated by the Law of Ukraine «On Protection of Animals from Cruelty» (№ 3447-IV of 21.02.2006) and the European Convention for the protection of vertebrate animals used for research and other scientific goals (Strasbourg, March 18, 1986).

All animals were divided into 5 groups: 1st – intact rats (n=8-10). This group of animals was injected intragastrically with 1% starch solution; 2-a – animals with thiolactone HHCy, which was caused by intragastric administration of HCy in the form of thiolactone at a dose of 100 mg/kg body weight in 1% starch solution once a day for 28 days (n=8-10). The dose, routes and duration of administration of thiolactone HCy are borrowed from the literature and did not cause the death of animals [12]; 3-a – animals with hyperthyroidism, which were administered intragastrically daily for 21 days by L-thyroxine at a dose of 200 μg/kg in 1% starch solution (n=8-10) [12]; 4-a – animals with thiolactone HHCy, which were daily administered intragastrically for 21 days by L-thyroxine at a dose of 200 μg/kg in 1% starch solution (n=8-10); 5-a – animals with hypothyroidism, which were administered intragastrically daily for 21 days by mercazolyl at a dose of 10 mg/kg body weight in 1% starch solution (n=8-10) [12]; 6-a – animals with thiolactone HHCy, which were daily administered intragastrically by mercazolyl at a dose of 10 mg/kg per 1% starch solution (n=8-10). Animals were deduced from the experiment 24 hours after the last administration of the selected substances.

The material was taken according to the generally accepted method. Pieces of the heart's left ventricle were fixed in 10% formalin solution for histological examination. Further material processing with next pouring into paraffin blocks was conducted by generally accepted methods [13]. Sections 4-6 μm thick were obtained on a rotary microtome AMR 400 and were stained with hematoxylin-eosin. It was studied and documented with the help of a light optical microscope with a MICROmed

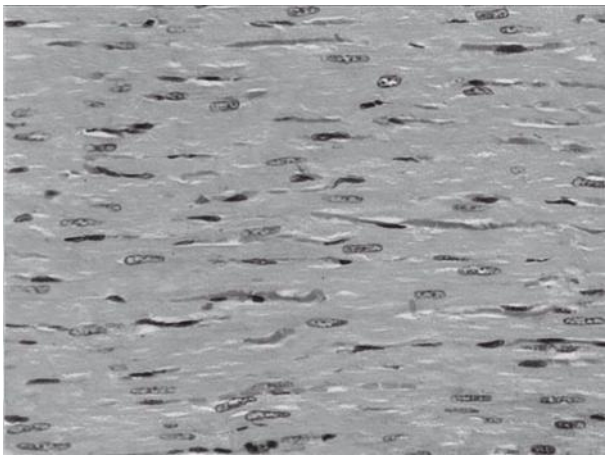

Figure 1 – Histological organization of the left ventricular myocardium of the intact rat. Longitudinal section of muscle fibers. Hematoxylin and eosin staining. Magnification: x200.

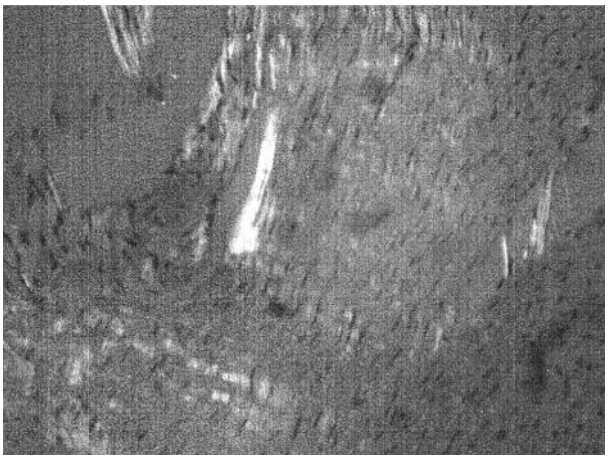

Figure 2 – Histological section of the left ventricle animal myocardium under the conditions of the simulated HHCy. Sporadic contractural changes of cardiomyocytes, myocytolysis of individual cells. Polarization microscopy. Magnification: x100.

SEO SCAN polarizer (Sumy, Ukraine) and a Vision CCD Camera.

Results of the research. Microscopic studies have indicated that the heart wall of intact animals is formed by three membranes – endocardium, myocardium, and epicardium. The thickest membrane is the myocardium, which is formed by striated muscle tissue. The heart muscle has the muscle fibers form that branch and anastomose with each other, forming a network. Loose fibrous connective tissue with nerves and blood vessels lies between them. Muscle fibers are formed by contractile (typical) cardiomyocytes that are interconnected by intercalated discs. Typical cardiomyocytes are rectangular in the longitudinal section of the heart muscle. The central cell part contains an oval, basophilic nucleus with one or two nucleoli **(fig. 1)**. Myofibrils form a transverse striation in the sarcoplasm, which indicates the orderly location of actin and myosin myofilaments in their composition.

There are moderately blood-filled arteries, veins, and vessels of the microcirculatory tract in the myocardium connective tissue. Somatic hemocapillaries are located in the tissue of the organ densely **(fig. 1)**.

Microscopic heart studies of II laboratory animals group, with simulated HHCy, were revealed myocardial vascularization disorders. Erythrocyte stasis and thrombosis have been found in many vessels. Increased permeability of vascular walls is accompanied by increased hydration of connective tissue, increased volume of connective tissue in the perivascular space and interstitium. Cardiomyocytes of muscle fibers are characterized by intercellular edema, destruction, and plasmolysis, the cytoplasm was moderately oxyphilic, without pronounced destructive changes only in some cardiomyocytes. Part of the muscle fibers has shown a contractural type of damage, which was manifested by increased anisotropy of the myofibrils A-disks, which were determined by polarization microscopy. Cardiomyocytes with signs of myocytolysis were detected sporadically **(fig. 2).** Small infiltrates of lymphocytes, macrophages and fibroblasts were detected in the stromal connective tissue **(fig. 3).**

Microscopic studies of the heart of the III experimental group laboratory animals, which simulated hyperthyroidism, have revealed signs of vascular insufficiency in the organ. There was an uneven blood supply to the myocardial vessels, some of which were full-blooded with erythrocyte concentrate and thrombosis. Perivascular and diapedetic hemorrhages were found. The relative volume of connective tissue was increased both in the perivascular space and

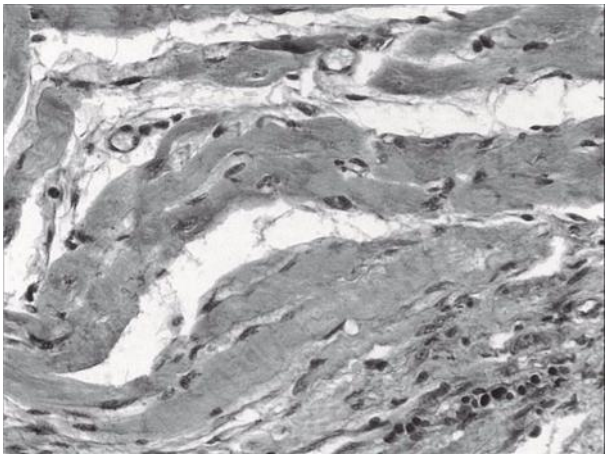

Figure 3 – Microscopic changes of the left ventricular animal myocardium under the conditions of the simulated HHCy. Swelling of stromal connective tissue, stretching of muscle fibers, area of histoleukocyte infiltration. Hematoxylin-eosin staining. Magnification: x200.

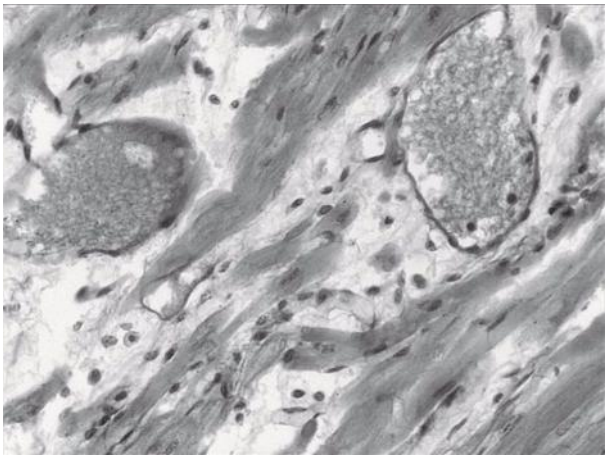

Figure 4 – Microscopic changes of the left ventricle myocardium of the animal's heart under the conditions of simulated hyperthyroidism. Myocardial muscle fibers, interstitial edema, and full blood vessels. Hematoxylin-eosin staining. Magnification: x200.

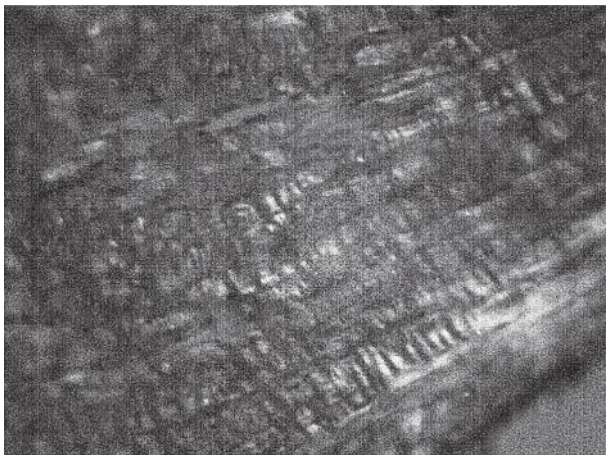

Figure 5 – Histological section of the animal myocardium left ventricle under the conditions of simulated hyperthyroidism. Contractural remodeling of cardiomyocytes. Polarization microscopy. Magnification: x200

between muscle fibers with myocardial hyperthyroidism **(fig. 4).**

Stratification of myocardial muscle fibers and inhomogeneous coloration of cardiomyocytes in their composition were detected, the sarcoplasm of these cells was compacted and was oxyphilic brightly, which is indicated about the presence of the contractile changes **(fig. 5)**. Intracellular edema, dystrophic changes, and foci of plasmolysis were found in cardiomyocytes **(fig. 4).**

Studies of the heart structural organization of group IV laboratory animals, which were simulated by hypothyroidism and HHCy, were revealed an increase of changes in muscle, and connective tissue components of organ. These changes occurred in the background of impaired vascularization of the organ. The dilatation and blood filling of vessels, which was accompanied by significant hemorrhages, were revealed **(fig. 6).** Increased interstitial edema was revealed. Lymphocytes, histiocytes, fibroblasts are identified in the connective tissue. Stratification of muscle fibers is there, in some of them the transverse striation was weak, a significant area of contractile changes and myocytolysis was formed **(fig. 7).**

Microscopic study of the myocardium of V group laboratory animals, which were simulated by hypothyroidism, was revealed hemodynamic disorders, which were manifested by dilatation and blood filling of venous ves-

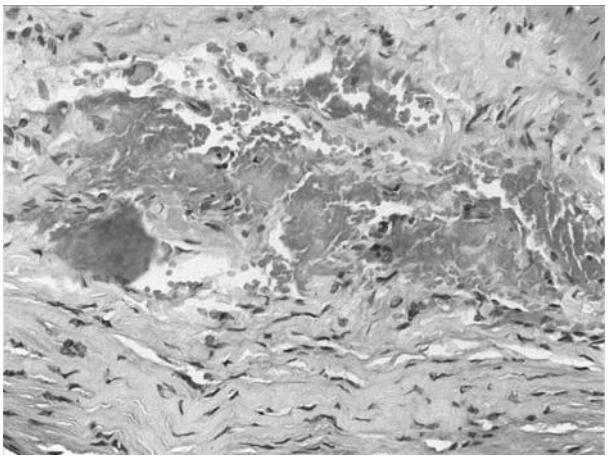

Figure 6 – Microscopic changes of the left ventricular myocardium of the animal in simulated hyperthyroidism and HHCy. Alteration and myocytolysis of cardiomyocytes in the composition of myocardial fibers, hemorrhage. Hematoxylin-eosin staining. Magnification: x200.

sels, erythrostasis, perivascular edema, local leukocyte infiltration of the interstitium. The relative volume of connective tissue has increased due to edema of the amorphous component. Cell hypertrophy was found in some muscle fibers. Small-droplet and hydropic dystrophy and the centers of plasmolysis were defined in many cardiomyocytes **(fig. 8).** Damage of the transverse myofibrils striation, moderate contractural changes, fiber fragmentation were found **(fig. 9).**

Microscopic studies of the heart of VI experimental group laboratory animals (combined effect of hypothyroidism and HHCy) were revealed the development of degenerative and atrophic changes in the organ wall in the background of significant vascular disorders. Significant swelling of the loose fibrous connective tissue was found both in the perivascular space and between the muscle fibers, which were delaminated and fragmented. Thinning and atrophy of cardiomyocytes, contractural changes, intensified myocytolysis processes are found **(fig. 10).** Histoleukocyte infiltrates and growth of collagen fibers were revealed in the interstitium. Destruction of walls of microcirculation vessels with the following hemorrhages was observed **(fig. 11).**

Discussion of research results. The results of our study have showed that HHCy was accompanied by

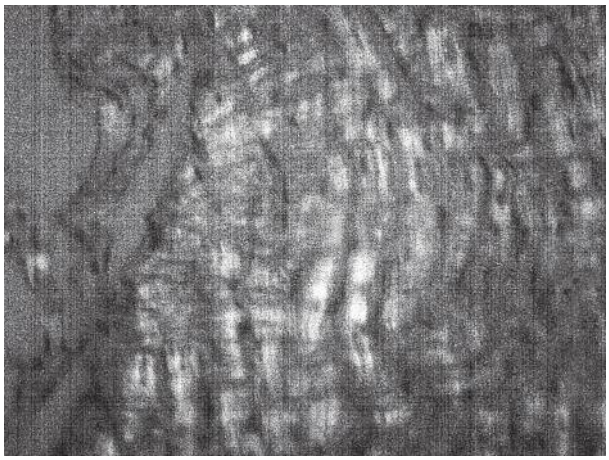

Figure 7 – Histological section of the left ventricular myocardium of the animal under the conditions of simulated hyperthyroidism and HHCy. Contractural remodeling, myocytolysis of cardiomyocytes. Polarization microscopy. Magnification: x 200.

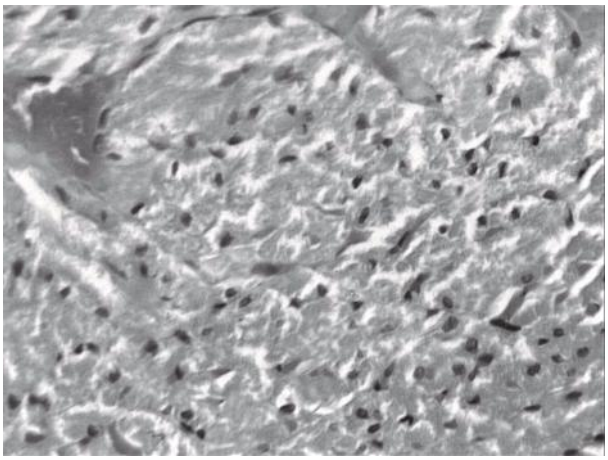

Figure 8 – Microscopic changes of the left ventricular myocardium under the conditions of simulated hypothyroidism. Alteration of myocardial muscle fibers, edema of the interstitium. Hematoxylin-eosin staining. Magnification: x200.

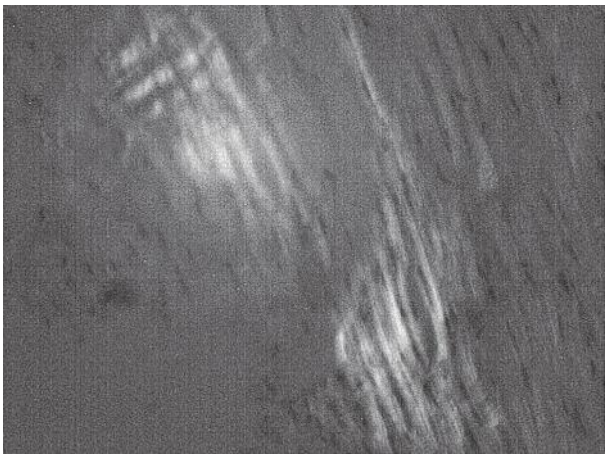

Figure 9 – Histological section of the left ventricle myocardium of the animal under the conditions of simulated hypothyroidism. Areas of contractile changes of cardiomyocytes, myocytolysis of some cells. Polarization microscopy. Magnification: x 100.

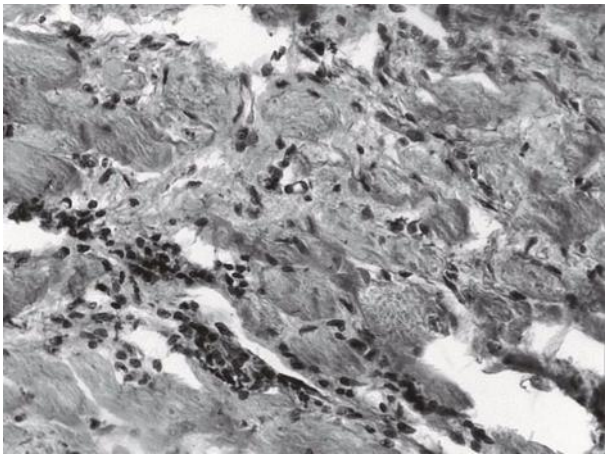

Figure 10 – Histological changes of the left ventricular myocardium under the conditions of simulated hypothyroidism and HHCy. Fragmentation and myocytolysis of cardiomyocytes in the composition of myocardial muscle fibers, leukocyte infiltration. Hematoxylin-eosin staining. Magnification: x200.

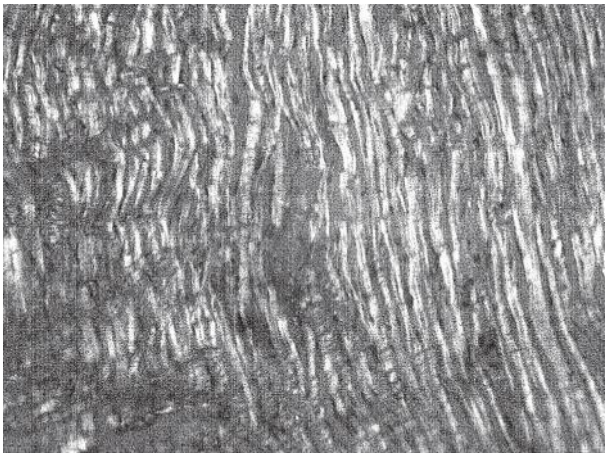

Figure 11 – Histological section of the left ventricular animal myocardium under the conditions of simulated hypothyroidism and HHCy. Contractural remodeling of cardiomyocytes, widespread myocytolysis of cells. Polarization microscopy. Magnification: x100.

changes in the myocardium of rats, in particular, there was a damage of blood vessels vascularization, erythrocyte stasis and thrombosis. Intercellular edema, destruction, and plasmolysis have been found in muscle fiber cardiomyocytes. Our results are consistent with the literature, in particular, in [14] it was shown that the high prevalence of atherosclerosis and high levels of HCy is associated with pronounced changes in the deformation properties of the left ventricular myocardium. The authors have concluded that the higher the level of HCy, is the more pronounced the atherosclerosis course and changes in the functional myocardium state. HHCy is harmed local contractile function in patients with coronary heart disease, which should be considered before surgery. Yeh, J. K et al. [15] have shown that HCy increases oxidative stress and consistently contributes to endothelial dysfunction and changes in NO-dependent vasodilation. Relating to coronary blood flow, feedback has also been demonstrated between HHCy and endothelium-dependent blood flow, especially in young patients [16]. It was also revealed a reverse relationship between mild HHCy and coronary heart disease, as atherosclerosis is accelerated the decrease in renal function, thus increasing plasma HCy levels [17].

It is known that hyperthyroidism is associated with increased heart rate, tachycardia, exercise intolerance, exercise breathlessness. We have found signs of vascular failure in animals with hyperthyroidism. Uneven myocardial vascular blood supply was found, some of which were full-blooded with erythrocyte sludge and thrombosis. Perivascular and diapedetic hemorrhages, stratification of myocardial muscle fibers, and heterogeneous coloration of cardiomyocytes were observed.

The study [18] has shown that patients with hyperthyroidism have an increased risk of atrial arrhythmia and heart failure, as prolonged thyroid hormone excess affects morphology and heart function negatively due to increased left ventricular mass, artery stiffness, and left atrial size. Autoimmune hyperthyroidism is often associated with autoimmune cardiovascular system damage (pulmonary arterial hypertension, myxomatous heart valve disease, and autoimmune cardiomyopathy). The influence of thyroid hormones on the heart and peripheral vascular system includes decreased systemic vascular resistance and diastolic blood pressure, as well as the increase of heart rate at rest, left ventricular contractility, and pulmonary arterial pressure. These combined effects increase cardiac output by 50–300% in overt hyperthyroidism [18], leading to right ventricular failure and left ventricular hypertrophy, increased left ventricular contractility, and ejection fraction [19].

A study of the structural organization of the laboratory animal`s heart with hyperthyroidism and HHCy has shown an increase in destructive changes in the muscular and connective tissue components of the organ. We have found dilatation and blood filling of vessels with significant hemorrhage, increased interstitial edema, and stratification of muscle fibers. The study [20] was shown that thyrotoxic cardiomyopathy, defined as myocardial damage is caused by toxic effects of excessive thyroid hormone, it leads to changes in myocyte energy production, increases intracellular metabolism, and contractile function of the myofibrils, and is manifested by left ventricular hypertrophy, dilatation of the heart chambers, heart failure, and diastolic dysfunction.

Hemodynamic disturbances were more apparent in the laboratory animal's myocardium with hypothyroidism than in rats with hyperthyroidism. In addition, muscle hypertrophy was observed in muscle fibers, and small-droplet and hydropic dystrophy were detected. The study [21] was found that hypothyroidism can affect heart contractility and damage heart muscle relaxation. Associated diastolic hypertension and sometimes concomitant coronary artery disease also affect myocardial diastolic function. Cardiac echocardiography is showed relaxation disorders in patients with overt and subclinical hypothyroidism. Damage of relaxation in subclinical hypothyroidism was confirmed by prolongation of the isovolumetric relaxation time and a decrease in the ratio of the transmitral flow rate [22]. This direction of changes leads to low cardiac output with a decrease in heart rate and stroke volume. Protein-rich pericardial and/or pleural effusion often occurs as a result of increased vascular permeability in hypothyroidism. The conversion of T_4 to T_3 decreases with advanced heart failure and after myocardial infarction shortly. As T_3 is a major regulator of gene expression in the myocardial muscle, it is thought that its reduction affects myocardial contractility and remodeling [23]. Low levels of free T_3 have also been linked to increased mortality in patients with heart disease [10].

Microscopic study of the rat's heart under the combined effects of hypothyroidism and HHCy has revealed the development of the most pronounced degenerative and atrophic changes in the myocardium on the background of significant vascular disorders in comparison with other groups of animals. Thinning and atrophy of cardiomyocytes were established. Histoleukocyte infiltrates, growth of collagen fibers, destruction of walls of microcirculation vessels with the subsequent hemorrhages were found in an interstitium. Muzaffar R. et al. [24] have conducted a study to assess the connection strength of elevated plasma concentrations of HCy in plasma as a risk factor for coronary heart disease. The average value of the HCy content in the plasma of patients with coronary heart disease was 22.33±9.22 μmol/l, while in the control group it was 12.59±3.73 μmol/l ($p<0.001$). The performed logistic regression indicates a strong association of coronary heart disease with HHCy (OR 7,45). The authors have concluded that elevated plasma HCy level is an independent risk factor for coronary heart disease, which is independent of common risk factors and can be used as an indicator to predict the future possibility of CVD.

Conclusions. Significant microscopic changes of stromal-vascular-parenchymal components of the organ are observed under the conditions of experimental HHCy, hyper-, and hypothyroidism in the myocardium of laboratory rats. Edema of the amorphous component of interstitial and perivascular connective tissue with the formation of extravascular histoleukocyte infiltrates has occurred in the background of vascular disorders and increased permeability of vascular walls. Remodeling of cardiomyocyte fibers is manifested by contractural changes, fragmentation, and intracellular myocytolysis. In the conditions of combined action of hyperthyroidism and HHCy and hypothyroidism and HHCy even more pronounced necrotic and degenerative changes of cardiomyocytes were occurred in the background of vascular insufficiency in the organ: damage to the vascular wall is manifested by hemorrhages and leukocyte inflammatory infiltrates; growth of collagen fibers, contractural changes of muscle fibers, significant myocytolysis of cardiomyocytes with stratification and lysis of myofibrils are revealed.

Prospects for further research. It is advisable to study the relationship between the ultrastructural state of the liver, kidneys, brain, and heart and changes in sulfur-containing amino acid metabolism in these organs and the concentration of thyroid hormones in the body, as well as and to study the effect of cofactors of enzymes of sulfur-containing amino acids (vitamins B_6, B_9, B_{12}, and betaine) on the ultrastructural condition of organs in rats in experimental hyper- and hypothyroidism.

References

1. Peng YP, Huang MY, Xue YJ, Pan JL, Lin C. Association of Hyperhomocysteinemia with Increased Coronary Microcirculatory Resistance and Poor Short-Term Prognosis of Patients with Acute Myocardial Infarction after Elective Percutaneous Coronary Intervention. Biomed Res Int. 2020 Jan 2;2020:1710452. DOI: 10.1155/2020/1710452.
2. Stangl GI, Weisse K, Dinger C, Hirche F, Brandsch C, Eder K. Homocysteine thiolactone-induced hyperhomocysteinemia does not alter concentrations of cholesterol and SREBP-2 target gene mRNAS in rats. Exp Biol Med (Maywood). 2007 Jan;232(1):81-7.
3. Vargas-Uricoechea H, Bonelo-Perdomo A, Sierra-Torres CH. Effects of thyroid hormones on the heart. Clin Investig Arterioscler. 2014;26(6):296-309. DOI: 10.1016/j.arteri.2014.07.003.
4. Timmis A, Townsend N, Gale CP, Torbica A, Lettino M, Petersen SE, et al. European Society of Cardiology: Cardiovascular Disease Statistics 2019. Eur Heart J. 2020 Jan 1;41(1):12-85. DOI: 10.1093/eurheartj/ehz859.
5. Agoston-Coldea L, Mocan T, Gatfosse M, Lupu S, Dumitrascu DL. Plasma homocysteine and the severity of heart failure in patients with previous myocardial infarction. Cardiol J. 2011;18(1):55-62.
6. He Y, Li Y, Chen Y, Feng L, Nie Z. Homocysteine level and risk of different stroke types: a meta-analysis of prospective observational studies. Nutr Metab Cardiovasc Dis. 2014 Nov;24(11):1158-65. DOI: 10.1016/j.numecd.2014.05.011.
7. Han L, Wu Q, Wang C, Hao Y, Zhao J, Zhang L, et al. Homocysteine, Ischemic Stroke, and Coronary Heart Disease in Hypertensive Patients: A Population-Based, Prospective Cohort Study. Stroke. 2015 Jul;46(7):1777-86. DOI: 10.1161/STROKEAHA.115.009111.
8. Brent GA. Mechanisms of thyroid hormone action. J Clin Invest. 2012 Sep;122(9):3035-43. DOI: 10.1172/JCI60047.
9. Gereben B, Zavacki AM, Ribich S, Kim BW, Huang SA, Simonides WS, et al. Cellular and molecular basis of deiodinase-regulated thyroid hormone signaling. Endocr Rev. 2008;29(7):898-938. DOI: 10.1210/er.2008-0019.
10. Biegelmeyer E, Scanagata I, Alves L, Reveilleau M, Schwengber FP, Wajner SM. T_3 as predictor of mortality in any cause non-critically ill patients. Endocr Connect. 2021 Jul 28;10(8):852-860. DOI: 10.1530/EC-21-0080.
11. Pingitore A, Chen Y, Gerdes AM, Iervasi G. Acute myocardial infarction and thyroid function: new pathophysiological and therapeutic perspectives. Ann Med. 2012 Dec;44(8):745-57. DOI: 10.3109/07853890.2011.573501.
12. Lin YH, Lin KH, Yeh CT. Thyroid Hormone in Hepatocellular Carcinoma: Cancer Risk, Growth Regulation, and Anticancer Drug Resistance. Front Med (Lausanne). 2020 May 22;7:174. DOI: 10.3389/fmed.2020.00174.
13. Horal's'kyy LP, Khomych VT, Konons'kyy OI. Osnovy histolohichnoyi tekhniky i morfofunktsional'ni metody doslidzhen' u normi ta pry patolohiyi. 2 vyd. Zhytomyr: "Polissya"; 2011. 288 s. [in Ukrainian].
14. Nykonenko OS, Chmul' KO, Nykonenko AO, Osaulenko VV, Yefymen NF. Prohnostychne znachennya rivniv homotsysteyinu ta vitaminu D u khvorykh na IKHS i mul'tyfokal'nyy ateroskleroz. Zaporiz'kyy medychnyy zhurnal. 2018;20(1):31-35. DOI: https://doi.org/10.14739/23101210.2018.1.121880. [in Ukrainian].

15. Yeh JK, Chen CC, Hsieh MJ, Tsai ML, Yang CH, Chen DY, et al. Impact of Homocysteine Level on Long-term Cardiovascular Outcomes in Patients after Coronary Artery Stenting. J Atheroscler Thromb. 2017 Jul 1;24(7):696-705. DOI: 10.5551/jat.36434.
16. Peng HY, Man CF, Xu J, Fan Y. Elevated homocysteine levels and risk of cardiovascular and all-cause mortality: a meta-analysis of prospective studies. J Zhejiang Univ Sci B. 2015 Jan;16(1):78-86. DOI: 10.1631/jzus.B1400183.
17. Rodondi N, Bauer DC, Cappola AR, Cornuz J, Robbins J, Fried LP, et al. Subclinical thyroid dysfunction, cardiac function, and the risk of heart failure. The Cardiovascular Health study. J Am Coll Cardiol. 2008 Sep 30;52(14):1152-9. DOI: 10.1016/j.jacc.2008.07.009.
18. Biondi B, Bartalena L, Cooper DS, Hegedüs L, Laurberg P, Kahaly GJ. The 2015 European Thyroid Association Guidelines on Diagnosis and Treatment of Endogenous Subclinical Hyperthyroidism. Eur Thyroid J. 2015 Sep;4(3):149-63. DOI: 10.1159/000438750.
19. Biondi B, Kahaly GJ. Cardiovascular involvement in patients with different causes of hyperthyroidism. Nat Rev Endocrinol. 2010 Aug;6(8):431-43. DOI: 10.1038/nrendo.2010.105.
20. Yeh JK, Chen CC, Hsieh MJ, Tsai ML, Yang CH, Chen DY, et al. Impact of Homocysteine Level on Long-term Cardiovascular Outcomes in Patients after Coronary Artery Stenting. J Atheroscler Thromb. 2017 Jul 1;24(7):696-705. DOI: 10.5551/jat.36434.
21. Kahaly GJ, Dillmann WH. Thyroid hormone action in the heart. Endocr Rev. 2005 Aug;26(5):704-28. DOI: 10.1210/er.2003-0033.
22. Roth GA, Huffman MD, Moran AE, Feigin V, Mensah GA, Naghavi M, et al. Global and regional patterns in cardiovascular mortality from 1990 to 2013. Circulation. 2015 Oct 27;132(17):1667-78. DOI: 10.1161/ CIRCULATIONAHA.114.008720.
23. Lisco G, Giagulli VA, Iovino M, Zupo R, Guastamacchia E, De Pergola G, et al. Endocrine system dysfunction and chronic heart failure: a clinical perspective. Endocrine. 2022 Feb;75(2):360-376. DOI: 10.1007/s12020-021-02912-w.
24. Muzaffar R, Khan MA, Mushtaq MH, Nasir M, Khan A, Haq IU, et al. Hyperhomocysteinemia as an Independent Risk Factor for Coronary Heart Disease. Comparison with Conventional Risk Factors. Braz J Biol. 2021 Sep 6;83:e249104. DOI: 10.1590/1519-6984.249104.

МОРФОЛОГІЧНІ ОСОБЛИВОСТІ МІОКАРДА ПРИ ГІПЕРГОМОЦИСТЕЇНЕМІЇ НА ФОНІ ПОРУШЕННЯ ФУНКЦІЇ ЩИТОПОДІБНОЇ ЗАЛОЗИ

Нечипорук В. М., Пентюк Л. О., Корда М. М.

Резюме. Серцево-судинні захворювання є основною причиною смертності у всьому світі. Відомо, що гормони щитоподібної залози регулюють метаболізм в усіх органах, в тому числі і в міокарді. Гіпергомоцистеїнемія добре відома як незалежний предиктор серцево-судинних захворювань.

Мета – встановити реорганізацію структурних компонентів міокарда за умов змодельованої ГГЦ на фоні гіпер- та гіпотиреозу.

*Об'єкт і методи дослідження***.** Тіолактонову ГГЦ моделювали введенням тваринам екзогенного ГЦ у вигляді тіолактону в дозі 100 мг/кг маси тіла один раз на добу протягом 28 діб. Гіпертиреоз моделювали шляхом щоденного введення L-тироксину в дозі 200 мкг/кг протягом 21-го дня, гіпотиреоз – щоденного введення мерказолілу в дозі 10 мг/кг протягом 21-го дня. Окремим групам тварин вводили L-тироксин і мерказоліл паралельно з ГЦ.

Результати дослідження. ГГЦ супроводжувалася деструктивними змінами у міокарді щурів. Встановлено порушення васкуляризації у судинах, виявлено еритроцитарні стази та тромбози. Серед кардіоміоцитів м'язових волокон встановлений інтерцелюлярний набряк, деструкція та плазмоліз. У тварин з гіпертиреозом були виявлені ознаки розвитку судинної недостатності в органі. Встановлено нерівномірне кровонаповнення судин міокарда. Виявлялися периваскулярні і діапедезні крововиливи, розшарування м'язових волокон. У тварин з гіпертиреозом та ГГЦ виявлено наростання деструктивних змін в м'язових та сполучнотканинних компонентах органу. Щурі з гіпотиреозом мали гемодинамічні порушення у міокарді, які проявлялись розширенням та кровонаповненням судин венозного русла, еритростазами, периваскулярним набряком, локальною лейкоцитарною інфільтрацією інтерстицію та збільшенням відносного об'єму сполучної тканини. Поєднаний вплив гіпотиреозу та ГГЦ призводив до більш виражених дегенеративних та атрофічних змін в стінці органу на тлі значних судинних порушень.

Висновки. В умовах експериментальної ГГЦ, гіпер- та гіпотиреозу в міокарді лабораторних щурів спостерігаються значні мікроскопічні зміни стромально-судинно-паренхіматозних компонентів органу. На тлі судинних розладів та підвищення проникності стінок судин відбувається набряк аморфного компоненту інтерстиційної та периваскулярної сполучної тканини з утворенням екстравазальних гістолейкоцитарних інфільтратів. Ремоделювання волокон кардіоміоцитів проявляється контрактурними змінами, їх фрагментацією та внутрішньоклітинним міоцитолізом. В умовах поєднаної дії гіпертиреозу і ГГЦ та гіпотиреозу і ГГЦ встановлені ще більш виражені некротичні та дегенеративні зміни кардіоміоцитів, що відбуваються на тлі судинної недостатності в органі: пошкодження судинної стінки проявляється крововиливами та лейкоцитарними запальними інфільтратами, виявляються розростання колагенових волокон, контрактурні зміни м'язових волокон, значний міоцитоліз кардіоміоцитів з розшаруванням та лізисом міофібрил.

Ключові слова: гіпертиреоз, гіпотиреоз, гіпергомоцистеїнемія, міокард.

MORPHOLOGICAL FEATURES OF THE MYOCARDIUM IN HYPERHOMOCYSTHINEMIA ON THE BACKGROUND OF THYROID DISORDERS

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Abstract. Cardiovascular diseases are the leading cause of death worldwide. It is known that thyroid hormones regulate metabolism in all organs, including the myocardium. Hyperhomocysteinemia (HHCy) is well known as an independent predictor of cardiovascular disease.

The aim – to define the reorganization of the structural components of the myocardium under conditions influence of HHCy against the background of hyper- and hypothyroidism.

Object and methods. HHCy was modeled by administering exogenous HCy to animals in the form of thiolactone at a dose of 100 mg/kg of body weight once a day for 28 days. Hyperthyroidism (intragastric L-thyroxine for 21 days 200 μg/ kg*day), hypothyroidism (thiamazole 10 kg*day) for 21 days. Separate groups of animals were injected with L-thyroxine and thiamazole in parallel with HCy.

Study results. HHCy was accompanied by destructive changes in the myocardium of rats. Violations of vascularization in the vessels were established, erythrocyte stasis and thrombosis were detected. Among the cardiomyocytes of muscle fibers, intercellular edema, destruction and plasmolysis were established. Animals with hyperthyroidism showed signs of vascular insufficiency in the organ. Established uneven blood supply to the vessels of the myocardium. Perivascular and diapedetic hemorrhages, stratification of muscle fibers was detected. Animals with hypertypiosis and HHCy showed an increase in destructive changes in the muscle and connective tissue components of the organ. Rats with hypothyroidism had hemodynamic disturbances in the myocardium, which were manifested by the expansion and blood filling of the vessels of the venous bed, erythrostasis, perivascular edema, local leukocyte infiltration of the interstitium, and an increase in the relative volume of the connective tissue. The combined effect of hypothyroidism and HHCy led to more pronounced degenerative and atrophic changes in the organ wall against the background of significant vascular disorders.

Conclusions. Experimental HHCy, hyper- and hypothyroidism in the myocardium of rats, significant microscopic changes in the stromal-vascular-parenchymal components of the organ are observed. Against the background of vascular disorders and increased permeability of the walls of blood vessels, edema of the amorphous component of the interstitial and perivascular connective tissue occurs with the formation of extravasal histoleukocytic infiltrates. Remodeling of cardiomyocyte fibers is manifested by contracture changes, their fragmentation, and intracellular myocytolysis. Under conditions of the combined action of hyperthyroidism and HHCy and hypothyroidism and HHCy, even more pronounced necrotic and degenerative changes in cardiomyocytes occurring against the background of vascular insufficiency in the organ were established: damage to the vascular wall is manifested by hemorrhages and leukocyte inflammatory infiltrates. fibers, significant myocytolysis of cardiomyocytes with stratification and lysis of myofibrils.

Key words: hyperthyroidism, hypothyroidism, hyperhomocysteinemia, myocardium.

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The Authors declare no conflict of interest.

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