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AGE CHARACTERISTICS OF MYOCARDIAL BLOOD SUPPLY IN COMORBID PATHOLOGY

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Understanding the age-related changes in myocardial blood supply under conditions of diabetes mellitus and stress will help reveal the pathway of diabetic cardiomyopathy, considering the age aspect. Therefore, the aim of our work is to investigate the age-related morpho-functional changes in the hemomicrocirculatory bed (HMB) of the myocardium in rats with experimental streptozotocin-induced diabetes mellitus (SDM) under conditions of chronic immobilization stress (CIS). The study used heart fragments and blood from 56 2-month-old and 6-month-old male white rats, which were divided into 3 groups: 1 group with comorbid pathology, including modeled SDM and CIS, 2 group with SDM, and 3 – control group. The material was collected 14^{th} and 56^{th} days from the start of the experiment. According to our findings, hyperglycemia, and stress on the 14^{th} day of the experiment lead to spasm of the arterioles of the HMB and a significant deterioration in their permeability, as evidenced by a likely increase in the Vongenwort index in the arterioles. On the 56^{th} days, in the experimental groups of 6-month-old rats, vacuolar dystrophy and coagulation necrosis of endotheliocytes and myocytes, focal destruction of capillary walls, thickening, and proliferation of their basement membrane, pronounced micro- and macroclasmatic changes, and capillarosclerosis are observed. In contrast, 2-month-old rats alongside destructive changes in HMB vessels show phenomena of neovascularization. Thus, SCD leads to the development of diabetic microangiopathy in the vessels of the myocardium of rats of different age groups. In animals with comorbid pathology, damage of HMB vessels are more pronounced on the 56^{th} day of observation and is manifested by: destruction of capillary walls, capillarosclerosis. In 2-month-old rats, alongside destructively changed capillaries, we found to former new vessels with a characteristic ultrastructure.

Keywords: *heart, heart failure, diabetic cardiomyopathy, diabetes mellitus, cardiovascular diseases, hemomicrocirculatory bed.*

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Introduction

On February 24, 2022, russia attacked Ukraine. The constant shelling of the entire territory of our country and the occupation of some regions have led to the fact that the majority of the population is under constant stress. No one can live in constant stress, as it can lead to chronic pathological processes, one of which is Diabetes Mellitus (DM), which causes great social and economic damage, associated with complications, disability and death. A significant place among the complications of diabetes is occupied by diabetic cardiomyopathy, which has no specific clinical signs and often develops without subjective symptoms [1–4]. Mortality from myocardial infarction in DM is twice as high as in other patients. Diabetes increases the absolute risk of coronary death in men by 2.5 times, and in women by 4.7 times, compared to the general population [5; 6]. The high incidence of atypical, painless forms of chronic Coronary Heart Disease (CHD) and myocardial infarction poses a high risk of "sudden death". According to the authors, almost one third of patients hospitalised with heart failure have diabetes mellitus [7; 8]. Some studies have shown that CHD and myocardial infarction are the main macrovascular diseases and causes of myocardial ischaemia and, consequently, myocardial dysfunction with reduced ejection fraction in diabetes [9]. Although the mechanism by which hyperglycaemia causes coronary vascular damage is not fully understood, oxidative stress, inflammation, and endothelial damage caused by hyperglycaemia, play a key role in the development of microvascular complications [10].

Considering the above, the **aim** of our study is to investigate the age characteristics of morpho-functional changes in the hemomicrocirculatory bed of the myocardium of rats with experimental streptozotocin-induced diabetes mellitus (DM) under conditions of chronic immobilization stress (CIS).

Material and Methods

56 two- and six-month-old white male rats were used for the study; they were divided into 3 groups: group 1 – animals with experimental comorbidity (20 rats of different age categories), which included simulated streptozotocin-induced (STZ-induced) DM and CIS; group 2 – animals with STZ-induced DM (20 rats of different age categories); group 3 – control animals (6 six-month-old rats and 10 two-year-old rats). STZ-induced DM was modelled by a single intraperitoneal injection of streptozotocin "SIGMA" (USA) according to our patented method [11], at the rate of 6 mg/100 g of body weight for six-month-old rats and 7 mg/100 g for two-month-old rats. CIS was simulated by placing the animal in a closed plastic container for 5 hours per day [12]. In group 1, STZ-induced DM was simulated and, starting from the 14th day of the experiment, CIS was modeled. The material was collected on the 14^{th} and 56^{th} days from the beginning of the experiment. To exclude the influence of the daily rhythm and biological activity on the metabolism of rats, the material was collected in the morning, before feeding. For daily measurement of glucose levels in the vivarium, we used a portable glucose meter "Accu-Chek Active" ("Roche Diagn. GH" (Germany)) with a standard set of test strips by taking a drop of blood from the tail vein of a rat by making superficial incisions in the tail area in the morning on an empty stomach. Animal studies were conducted in certified laboratories: "Educational and Scientific Laboratory of Morphological Analysis", on the basis of the Centre of Bioelementology of the Ivano-Frankivsk National Medical University, in the laboratory "Diameb". Experiments on rats were carried out in compliance with all ethical requirements and in accordance with the provisions of the Euro-

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pean Convention for the Protection of Vertebrate Animals Used for and Other Scientific Purposes (Strasbourg, 1986), Council Directive 86/609/EEC (1986), the Law of Ukraine "On Protection of Animals from Cruelty" dated December 15, 2009 and orders of the Ministry of Health of Ukraine No.690 dated September 23, 2009, No.616 dated August 03, 2012 (expert opinion of the Ethics Committee of the Ivano-Frankivsk National Medical University, protocol No.111/19 from 11.19.2019).

Immediately after the animals were euthanised and blood was drawn into test tubes at the Centre for Bioelementology of the Ivano-Frankivsk National Medical University, glucose was determined by the glucose oxidase method, using a set of reagents manufactured by "GLUCOZA-FCD" (Ukraine). The level of glycated haemoglobin and cortisol in the blood was determined in the laboratory "Diameb".

Histological (haematoxylin and eosin staining, Masson's trichrome staining), electron microscopic, biochemical and statistical methods of investigation were used. When sampling the myocardium of the ventricles for electron microscopic examination, which was performed according to the generally accepted method, the rules of excision speed and atraumatisation of the myocardium during cutting into pieces, were observed [13].

For morphometric studies, photographs of histological sections were used (the field of view of the Leica DM 750 light microscope was photographed using a digital CCD camera with a 1200×1600 magnification and saved in *.tif format). Morphometry was performed using ImageJ software version 1.47t. Computer data processing was performed using the statistical package Stat.Soft.Inc; Tulsa, OK, USA; Statistica 10, USA. The sample parameters presented in the tables and text below have the following designations: M – sample mean, SD – standard deviation, n – sample size (the size of the group under analysis), and p – the level of statistical significance achieved.

Results and Discussion

On the 14th day of the experiment, the level of glucose and HbA1c in the blood of six-month-old rats in group 1 is the highest, compared to the control group and is (15.21±1.33) mmol/l ($p<0.001$) and (7.78±±0.58)% ($p<0.01$); in group 2 – (13.72±±1.53) mmol/l ($p<0.001$) and (6.08±0.45)% ($p<0.01$); in group 3 – (4.85±0.63) mmol/l and (1.78±0.18)%. In two-month-old animals, the glucose and HbA1c levels were as follows: in group 1 – (15.04±1.56) mmol/l and (7.18±0.37)% ($p<0.05$); in group 2 – (14.03±1.06) mmol/l and (7.09±0.51)% ($p<0.05$); in group 3 – (3.21±0.31) and (2.02±0.19)%. Such biochemical changes in groups 1 and 2 indicate the development of STZ-induced DM of moderate severity. The level of cortisol in the blood was significantly higher in all studied groups of animals compared to the control values, and accordingly was the following one in six-month-old rats: in group 1 – (32.17±±2.14) ng/ml; in group 2 – (18.29±2.27) ng/ml; in the control group – (10.06±0.98) ng/ml; in two-month-old rats: in group 1 – (48.5±2.19) ng/ml; in group 2 – (41.01±±3.12) ng/ml; in the control group – (11.45±±1.13) ng/ml (in all cases $p<0.05$, compared to the control values).

On the 14th day of the experiment, in groups 1 and 2 of rats of different ages, hyperemia of capillaries, venules, and veins is observed, while in the supply link of the hemomicrocirculatory system, most vessels have a slit-like space due to their spasm. According to the morphometric analysis, the area of arterioles significantly decreases in groups 1 and 2 due to the decrease in the area of their lumen (*Table 1*). This morphometric rearrangement of arterioles leads to a sharp decrease in their carrying capacity and is confirmed by a significant increase in Wagenworth index (WI) in group

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Table 1. Morphometric characteristics of the vessels of the hemomicrocirculatory bed of the myocardium in rats on the 14th day of the development of comorbid pathology

Group of animals	Micro-hemo-vessels under study	Vessel area (μm^2)	Lumen area (μm^2)	Wall area (μm^2)	WI, %
six-month-old rats					
1	arteriole	234.12±20.31*	46.58±7.26*,α	187.54±11.28	402.62±39.15*,α
	capillary	19.11±1.48	8.93±0.95	10.18±1.07	114.11±9.47
2	arteriole	241.48±189.12*	56.35±7.89*	185.13±12.39	328.53±27.64*
	capillary	19.06±1.23	8.68±1.04	10.38±1.32	119.58±10.25
3	arteriole	331.23±21.34	98.24±7.35	232.99±13.57	237.16±21.04
	capillary	18.56±1.17	8.42±1.14	10.44±1.35	123.99±11.48
two-month-old rats					
1	arteriole	190.36±14.99*	36.98±4.13*,α	153.38±12.3	417.36±36.38*
	capillary	12.59±1.39	5.57±0.46	7.01±1.11	125.92±17.05
2	arteriole	198.61±7.11*	41.04±3.40*	157.56±6.39	386.26±36.21*
	capillary	11.53±1.25	5.44±0.40	6.09±1.27	112.79±27.47
3	arteriole	224.42±13.57	67.32±4.58	157.±10.96	324.02±18.46
	capillary	12.06±1.04	5.96±1.02	6.10±0.86	105.34±24.74

Note: *$p<0.05$ – significance of values compared to group 3;
$^{\alpha}p<0.05$ – significance of values between groups 1 and 2.

1 by 1.7% and 1.3%, respectively, and in group 2 – by 1.4% and 1.2% compared with the control values (*Table 1*). At the same time, no changes in the capillary link were detected (*Table 1*). Such changes in microcirculation are caused by metabolic changes in the blood and high levels of counterinsular hormones, in particular cortisol [14].

At the ultrastructural level, the peculiarities of the structural rearrangement of endothelial cells in the capillaries of two-month-old rats were revealed. Thus, in six-month-old rats in each of the groups, the capillary lumen is limited by "light" and "dark" endotheliocytes. Light-colored endotheliocytes have a matrix of moderate electron-optical density and a normal structure, while dark endotheliocytes are characterized by an electron-dense matrix and poorly differentiated organelles.

In two-month-old rats of groups 1 and 2, the vast majority of capillaries showed increased electron-optical density of capillaries with numerous pinocytotic vesicles (*Fig. 1, a, b*), which may indicate an increase in trans-endothelial exchange in simulated pathologies. In addition, in two age groups of animals, on the 14th day of the experiment, in groups 1 and 2, erythrocyte sludge, adhesion of erythrocytes and platelets to the lumenal surface of endotheliocytes, and microclasmatosis appeared in the capillaries (*Fig. 1, a, b*). Such changes in the morphological structure of capillaries lead to a deterioration in blood flow, and as a consequence, to hemic hypoxia of tissues.

Based on the obtained results, these values are higher in groups 1 and 2, compared to the control group, but the glucose level increases unreliably, while HbA1c continues to increase. Such changes indi-

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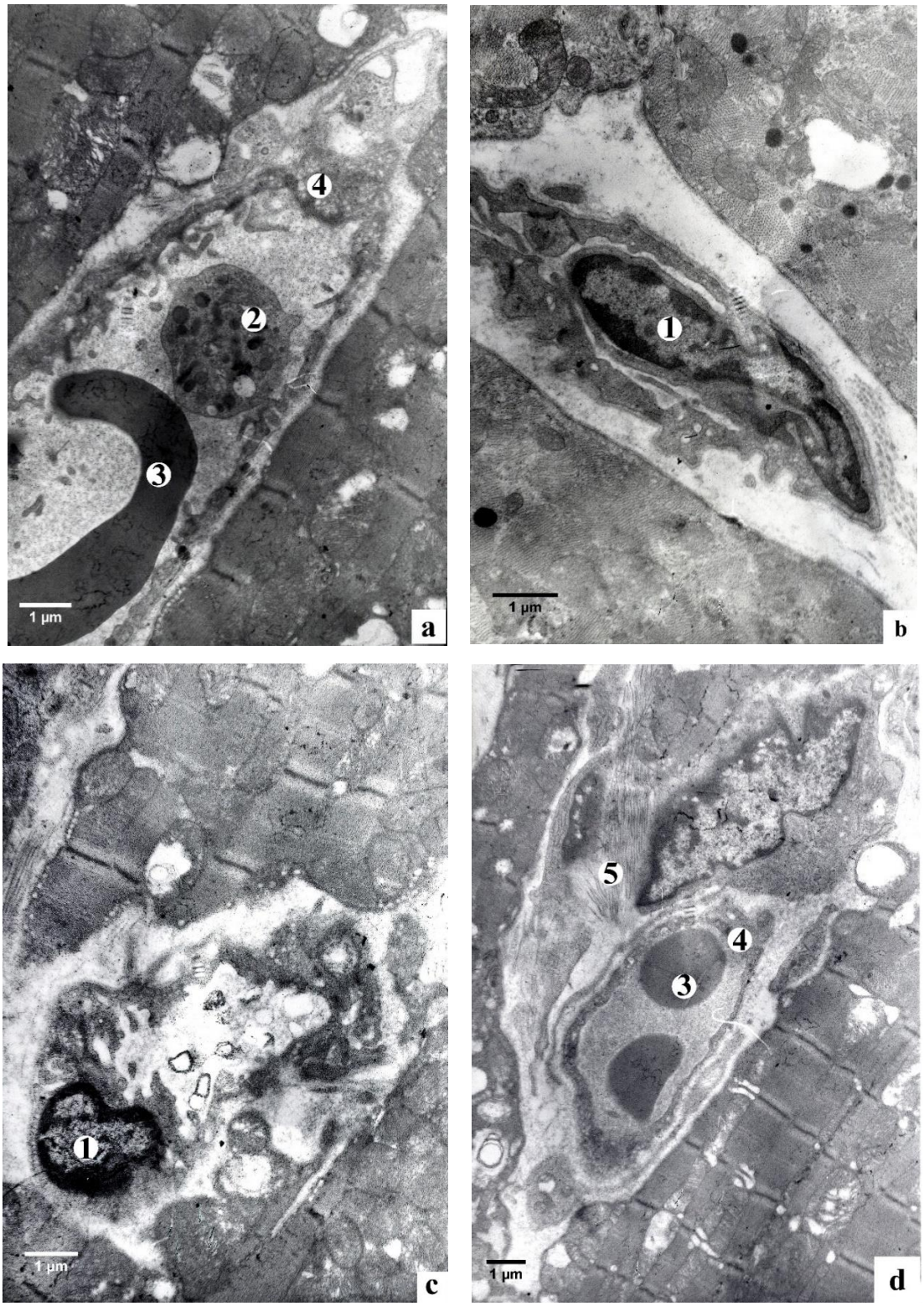

Fig. 1. Morpho-functional reconstruction of myocardial capillaries of two-month-old rats on the 14th (a, b) and 56th (c, d) days of the experiment. Electron micrographs.

Designation: 1 – endotheliocyte nucleus, 2 – platelet, 3 – erythrocyte, 4 – micropinocytic vesicles, 5 – collagen fibres.

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cate the development of decompensated DM of moderate severity. The level of cortisol in the blood was significantly higher in all studied groups in two-month-old and six-month-old animals compared to the control values and was as follows: in group 1 – (20.16±2.17) ng/ml and (14.17±2.14) ng/ml (in all cases $p<0.05$); in group 2 – (24.16±2.09) ng/ml and (19.63± ±2.18) ng/ml (in all cases $p<0.05$); in the control group – (10.23±0.96) ng/ml (10.06± ±0.98) ng/ml. At the same time, comparing with the previous term of the experiment, the level of cortisol in the blood of all experimental groups of animals is likely to decrease (in all cases $p<0.05$) (*Table 2*).

In groups 1 and 2 of rats of different ages, the hyperemia of all micro-hemo-vessels is observed (*Fig. 2*) as a result of their overflowing with erythrocyte sludge and microthrombi. At the same time, the area of all vessels of the hemomicrocirculatory bed increases compared with intact values, which leads to an increase in WI in the arterioles of two groups both in comparison with the control and with the previous period of the experiment (in all cases $p<0.05$).

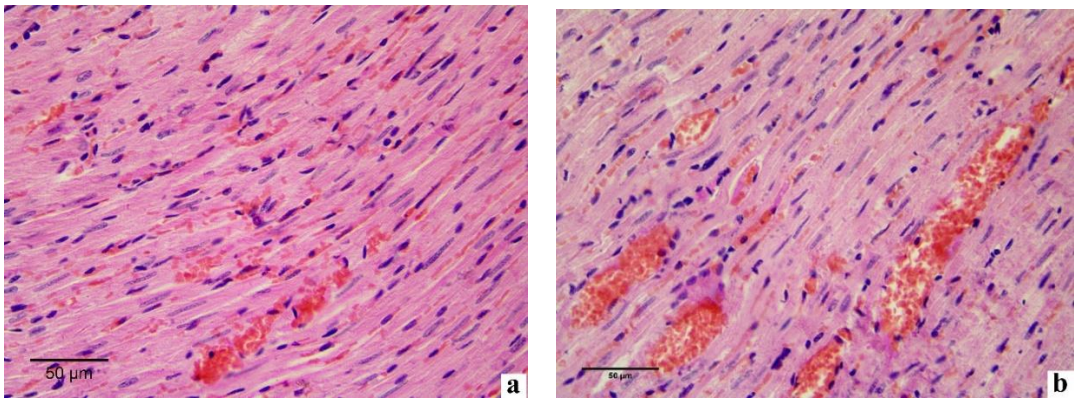

Fig. 2. Hyperemia of myocardial micro-hemo-vessels in two-month-old (a) and six-month-old (b) rats.

Table 2. Morphometric characteristics of the vessels of the hemomicrocirculatory bed of the myocardium in rats on the 56th day of the development of comorbid pathology

Group of animals	Micro-hemo-vessels under study	Vessel area (μm²)	Lumen area (μm²)	Wall area (μm²)	WI, %
six-month-old rats					
1	arteriole	344.12±20.31	45.58±7.26*	298.54±11.28*,#	654.98±37.1*#,α
	capillary	26.38±5.72*#	5.53±0.92*#	20.85±2.67*#	377.03±13.47*,#
2	arteriole	341.48±18.12	51.35±7.89*	290.13±10.38*	565.01±27.13*
	capillary	25.14±5.12*	5.24±0.92*,#	19.90±3.52*#	379.77±15.13*,#
3	arteriole	326.17±31.12	89.16±8.12	237.01±31.53	265.82±36.05
	capillary	19.27±2.54	8.39±1.27	10.88±2.23	129.68±7.82
two-month-old rats					
1	arteriole	320.46±15.63*,#,α	43.16±3.7*#,α	277.29±16.44*,#,α	647.76±76.95*,#,α
	capillary	24.33±5.5*#α	5.81±1.45*,#	18.52±4.12*#α	321.09±28.42*,#,α
2	arteriole	300.32±14.72*#	51.64±5.44*,#	248.68±11.37*,#	485.51±45.63*,#
	capillary	17.85±4.22*,#	5.05±1.42*#	12.80±3.20*#	260.05±58.01*,#

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Continuation of Table 2

Group of animals	Micro-hemo-ves-sels under study	Vessel area (μm^2)	Lumen area (μm^2)	Wall area (μm^2)	WI, %
3	arteriole	288.37±20.02	75.81±4.30	212.56±15.83	280.14±7.06
	capillary	15.65±3.21	7.59±1.49	8.06±2.12	107.64±25.71

Notes: $^{*}p<0.05$ – significance of values compared to group 3;
$^{\#}p<0.05$ – significance of values with the previous study period within the same age group;
$^{\alpha}p<0.05$ – significance of values between groups 1 and 2.

At the ultrastructural level, animals of different age groups show pronounced signs of diabetic microangiopathy, including hemorheological disorders and damage to the vascular wall (*Fig. 3*). Hemorheological disorders are manifested by erythrocyte sludge in the lumen of micro-hemo-vessels and microthrombi (*Fig. 3, b*), adhesion of erythrocytes and platelets to the lumenal surface of endotheliocytes, and pronounced microclasmatosis (*Fig. 3, a*). In endotheliocytes and myocytes, vacuolar dystrophy and colliquative necrosis are noted. In animals of different ages of group 1, focal desquamation of endotheliocytes and exposure of the basement membrane, partial and complete destruction of hemocapillaries (*Fig. 1, c*) and capillary sclerosis (*Fig. 1, d*) were observed in micro-hemo-vessels.

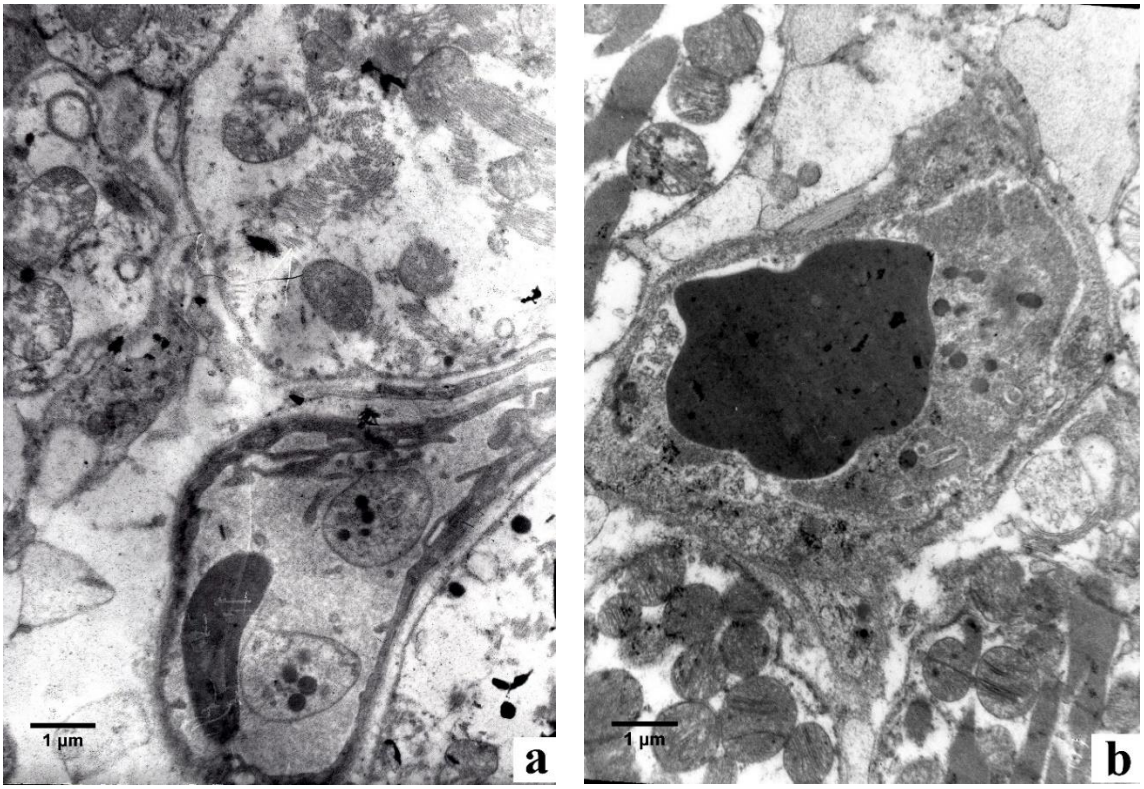

Fig. 3. Pronounced microclasmatosis (a) microthrombus in the lumen of the capillary (b) of the six-month-old rat in group 1 on the 56th day of the experiment. Electron micrographs.

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According to the results of our studies, from the 14th day of the development of streptozotocin-induced diabetes, we observe the first manifestations of diabetic microangiopathy, which are demonstrated by hemorheological disorders of microcirculation. Such changes are associated with various factors. First of all, these are metabolic changes that lead to glycation of hemoglobin and, as a consequence, to changes in the shape of red blood cells and their surface S-charges [15], which promotes true capillary stasis, sludge and agglutination of erythrocytes [16] It is known that in DM, glycosylation end products play a driving role in the development of vascular damage through the induction of oxidative stress and inflammation [17]. Glycosylation end products directly suppress the production of nitric oxide (NO) by endothelial cells and increase endothelial permeability, promoting the destruction of endothelial glycocalyx and disrupting tight junctions between endothelial cells [18; 19]. The end products of glycosylation can also activate endothelial cells, which leads to the expression of prothrombotic factors and the initiation of a cascade of coagulation mechanisms and formation of microthrombi [20], which we found in myocardial micro-hemo-vessels on the 56th day of the experiment. In addition, the end products of glycosylation interact with their cellular receptors, such as RAGE, to promote the production of active oxygen species (AOS) and activation of the nuclear factor-κB (NF-κB) signalling pathway, which lead to endothelial cell death through pyroptosis [21]. Glycosylation end products trigger a chain reaction of activation of pro-inflammatory cytokines, chemokines and adhesion molecules, promoting the migration of inflammatory cells and the continuation of inflammation in the vascular wall [22]. The end products of glycosylation can also promote the proliferation and migration of vascular smooth muscle cells, contributing to neointima formation and arterial remodelling in diabetes. They trigger the activation of mitogen-activated protein kinases and the regulation of growth factors, such as platelet-derived growth factor and transforming growth factor β (TGF-β), which stimulate myocyte proliferation and migration [23; 24], which led to a significant thickening of the arterial wall in animal groups 1 and 2 on the 56th day of the experiment in our studies. The end products of glycosylation also increase myocyte adhesion to the extracellular matrix by increasing the expression of integrins and other cell adhesion molecules [25], which leads to fibrosis of micro-hemo-vessels, according to our studies.

In our studies, we also noted the death of endothelial cells in two ways: apoptosis and necrosis. At the same time, it should be noted that in two-month-old rats, endotheliocyte apoptosis processes prevailed, and newly formed capillaries with certain morphological characteristics were detected [16]. According to other authors, the death of endotheliocytes in diabetes is considered a key factor contributing to vascular endothelial damage and can occur through apoptosis, autophagy and necrosis [22].

Conclusions

DM leads to the development of diabetic microangiopathy in the myocardial vessels of rats of different age groups. In animals with comorbid pathology (STZ-induced DM and CIS), hemorheological disorders and lesions of the microcirculatory vessels are more pronounced on the 56th day of observation and are manifested by capillary wall destruction, capillary sclerosis, and proliferation of the intima of arterioles. In two-month-old rats, along with destructively changed capillaries, we found newly formed ones with a characteristic ultrastructural structure.

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Prospects for further research

Further comprehensive studies of the molecular mechanisms of endothelial dysfunction of myocardial micro-hemovessels and cardiomyocytes in comorbid pathology in animals of different ages are promising, which will allow pathogenetic substantiation of new methods of treatment of diabetic cardiomyopathy and improvement of existing treatment regimens.

Conflict of interests is absent.

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ВІКОВІ ОСОБЛИВОСТІ КРОВОПОСТАЧАННЯ МІОКАРДА ПРИ КОМОРБІДНІЙ ПАТОЛОГІЇ

Знання вікових особливостей змін кровопостачання міокарда за умов цукрового діабету і стресу дозволить розкрити патоморфогенез діабетичної кардіоміопатії з врахуванням вікового аспекту. Тому метою нашої роботи є дослідити вікові особливості морфофункціональних змін гемомікроциркуляторного русла (ГМЦР) міокарда щурів при експериментальному стрептозотоциновому ЦД (СЦД) за умов хронічного іммобілізаційного стресу (ХІС). Матеріалом для дослідження слугували шматочки серця і кров 56-ти 2-місячний і 6-місячних білих щурів-самців, які розподілялися на 3 групи: 1 група із коморбідною патологією, що включала в себе модельований СЦД та ХІС, 2 група із СЦД, 3 група контрольні тварини. Матеріал забирали через 14 і 56 днів від початку експерименту. За даними наших досліджень гіперглікемія і стрес на 14-ту добу експерименту призводять до спазму приносних судин ГМЦР та погіршення їхньої пропускної здатності в рази що підтверджується вірогідним збільшенням індексу Вогенворта в артеріолах. На 56 добу експерименту гіперглікемія та високі рівні HbA1c призводять до розвитку діабетичної мікроангіопатії, яка проявляється гемореологічними порушеннями кровотоку та деструктивними змінами стінки судин ГМЦР. У дослідних групах 6-міс. щурів спостерігаються: вакуольна дистрофія та коліквационний некроз ендотеліоцитів і міоцитів, вогнищеве руйнування стінки капілярів та потовщення і проліферація їхньої базальної мембрани, капіляросклероз. Натомість у 2-міс щурів поряд із декструктивними змінами в судинах ГМЦР міокарда ми спостерігали явища неоваскулогенезу. Отже, СЦД призводить до розвитку діабетичної мікроангіопатії в судинах міокарда щурів різної вікової групи. У тварин з коморбідною патологією ураження судин ГМЦР є більш вираженими на 56 добу спостереження, зокрема у 6-міс щурів.

Ключові слова: *серце, серцева недостатність, діабетична кардіоміопатія, цукровий діабет, серцево-судинні захворювання, гемомікроциркуляторне русло*.

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