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Morphometric changes in the heart of rats with alloxan and streptozotocin diabetes

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ABSTRACT

In diabetes mellitus (DM), the ability of the myocardium to fully relax and fill with blood during diastole is impaired. Clinical observations by various authors confirm the presence of myocardial hypertrophy in patients with diabetes; in particular, an increase in the thickness of its posterior wall and interventricular septum has been established. In this regard, of undoubted interest is the study of the relationships between the frequency, structure, and severity of pathogenetic morphometric disorders of the heart in animals with experimental models of alloxan and streptozotocin diabetes. This study aimed to study morphometric changes in the heart in animals at different stages of development using models of experimental alloxan and streptozotocin diabetes. In this study, 450 rats with experimental diabetes were studied (intravenous administration of alloxan 35 mg kg^{-1}): **Model 1**: alloxan diabetes (group A): divided into subgroups: A_1: 6 months of observation (50 animals in each subgroup); A_2: 12 months; A_3: 24 months; **Model 2**: streptozotocin diabetes (group C): C_1: 6 months; C_2: 12 months; C_3: 24 months. CI: control group of intact rats: CI_1: 6 months (30 individuals per subgroup); CI_2: 12 months; KI_3: 24 months. They received a single injection of sterile saline solution into the femoral vein. Morphometric studies, volumetric ratios of tissue components were determined using an ocular measuring grid for cytohistostereometric studies. Avtandilova Statistical methods were used for studying the significance of the linear correlation coefficient (Pearson) and the rank coefficient (Spearman), then checked based on Student's t-test. In this study, upon extraction, the animal's heart was processed, dried, and weighed on a torsion balance. Weight in animals KI_1 heart weight was 3.5 g with a total weight of 195.4 g. In animals with intravenous administration of alloxan, the heart weight ($p < 0.05$) was in the range of 3.7-3.9 g with a total weight of 194.4 -195.7 g in streptozotocin diabetes, the weight of rats heart ($p < 0.05$) was 4.0-4.1 g with a total weight of 193.2-193.5 g. In a morphometric study of experimental animals' right and left ventricles and pulmonary arteries, the indicators were higher in group A_3. The volume of right ventricle in alloxan-induced diabetes was significantly ($p < 0.05$) greater than in the control groups. In the case of morphometric indicators of the rats heart with streptozotocin diabetes, pronounced ultrastructural changes distinguished cardiomyocytes. Lysis of cristae and outer mitochondrial membranes with the formation of myelin figures and dense protein bodies, were observed for alloxan diabetes at 24 months. Processes of hypertrophy of cardiomyocytes prevailed; nuclei volume increased ($p < 0.05$) by 34.6%, and euchromatin content and mitochondria increased by 23.8%.

Keywords: Experimental diabetes mellitus: Alloxan, Streptozotocin; Morphometric parameters, Heart.
Article type: Research Article.

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INTRODUCTION

According to WHO, there are more than 200 million people with diabetes in the world (De Fronzo 2009; Alekseenko & Drobot 2012; Wu *et al*. 2014; Preethikaa & Brundha 2018). There are many publications in the literature about micro- and macrovascular complications of diabetes mellitus (Rosenstock *et al*. 2005; Volkova *et al*. 2012; Medovshchikov *et al*. 2020; Sivasankari & Manivannan 2023). The main causes of death in patients with diabetes (76%) are cardiovascular diseases. Experimental and clinical studies have shown that in diabetes mellitus (DM), specific diabetic cardiomyopathy more often develops, in addition to the development of heart failure after myocardial infarction in the presence of relatively well-preserved systolic function of the heart (Sumin *et al*. 2018). The presence of myocardial hypertrophy in patients with diabetes, in particular, an increase in the thickness of its posterior wall and interventricular septum, has been established. There is an opinion that myocardial mass decreases with the decompensation of diabetes and is restored under the influence of the normalization of metabolism (Kornienko *et al.* 2015; Pavlikova *et al.* 2020; Eshniyazov *et al.* 2020). In the pathogenesis of an increase in myocardial mass in diabetes, specific (dystrophic) changes in the cardiac myocyte under the influence of metabolic disorders are important. A known role in the genesis of cardiomegaly is played by diffuse vascular damage in the form of diabetic microangiopathy, impaired neurohumoral regulation of cardiac activity, and early development of coronary sclerosis. The listed factors contribute to the development of myocardial hypoxia and its compensatory hyperfunction. Increased work of the heart leads to its hypertrophy, which causes an even greater oxygen deficiency. In this regard, of undoubted interest is the study of the relationships between the frequency, structure, and severity of pathogenetic morphometric disorders of the heart in animals with experimental models of alloxan and streptozotocin diabetes (Szkudelski 2001; Nikulina *et al.* 2011; Lomaeva *et al.* 2013; Kelechi *et al.* 2014; Nwauche *et al.* 2014; Kahn *et al.* 2014; Ravi *et al.* 2017; Preethikaa & Brundha 2018; Rekha *et al.* 2020; Jadhav *et al.* 2020; Mohammed *et al.* 2021;Natarajan *et al.* 2024; Abarnadevika *et al.* 2024; Supomo *et al.* 2024).

MATERIALS AND METHODS

Four hundred fifty rats with experimental diabetes were studied (intravenous administration of alloxan 35 mg kg^{-1}): The animals were intravenously injected with alloxan 35 mg kg^{-1}, and one model of alloxan diabetes, group A, was created. After 14 days, animals with persistent diabetes were divided into three subgroups of 50 animals each: subgroup A_1, observation period of 6 months, A_2: 12 months, and A_3: 24 months. The second group of animals was intravenously injected with streptozotocin (30 mg kg^{-1}), and a 2nd model of streptozotocin diabetes was created (group C), which was divided into subgroups at the same observation periods of 50 animals each: subgroup C_1: 6 months' follow-up, C_2: 12 months and C_3: 24-month. The CI control included intact animals of the same age groups, 30 animals in each group: subgroup CI_1: 6 months of observation, CI_2: 12 months, and subgroup CI_3: 24 months. Control animals were injected once into the femoral vein with a sterile saline solution equal to the diabetogenic solution's volume, subject to the same antiseptic rules.

Morphometric research: The volumetric ratios of tissue components were determined using an ocular measuring grid for cytohistostereometric studies by Avtandilov using counting points that randomly coincide with the structures being studied, according to the formula: V = m/n, where m is the number of points that accounted for a certain histostructure, n is the total number of counted points per section. To obtain representative results, initially, in each case, the required number of points with a 95% confidence interval was determined using the formula.

Statistical research methods

The obtained data were processed using the variation statistics method. The arithmetic sample mean (M), standard deviation (δ), and arithmetic mean error (m) were determined. The significance of the differences was assessed using the Student's t-test. The relationship between quantitative characteristics was studied using correlation analysis. The significance of the linear correlation coefficient (Pearson) and rank coefficient (Spearman) were checked based on the Student's t-test. To quantify the closeness of the connection, the correlation coefficient r was used, which is calculated in Excel using the fx function, followed by statistical functions and the CORREL function.

RESULTS AND DISCUSSION

The animal's heart was processed, dried, and weighed on a torsion balance upon removal. In animals KI_1, the heart weight was 3.5 g, and the total weight was 195.4 g. In animals with intravenous administration of alloxan, the heart weight ($p < 0.05$) was in the range of 3.7-3.9 g with a total weight of 194.4- 195.7 g. In streptozotocin

diabetes, the heart weight ($p < 0.05$) was 4.0-4.1 g with a total weight of rats of 193.2-193.5 g. The results of changes in the relative weight of the heart are illustrated in Table 1.

Table 1. Changes in the weight of rats and the heart of experimental animals (M ± m).

Subgroup of animals	Mass indicator, g	
	relative heart mass	mass of laboratory rats
АИТ1 (n = 30)	4.5 ± 0.04&	184.4 ± 1.1
АИТ2 (n = 30)	4.4 ± 0.03#	186.8 ± 1.4
АИТ3 (n = 30)	4.2 ± 0.04 ×	188.3 ± 1.2
А1 (n = 50)	3.9 ± 0.03*	195.7 ± 1.6
А2 (n = 50)	3.8 ± 0.02°	194.4 ± 1.3
А3 (n = 50)	3.7 ± 0.03+	195.1 ± 1.2
С1 (n = 50)	4.0 ± 0.04	193.2 ± 1.6
С2 (n = 50)	4.1 ± 0.04°	193.4 ± 1.6
С3 (n = 50)	4.0 ± 0.03+	193.5 ± 1.4
КИ1 (n = 30)	3.2 ± 0.02	208.8 ± 1.3
КИ2 (n = 30)	3.4 ± 0.03	209.8 ± 1.2
КИИ1 (n = 20)	3.5 ± 0.03	195.4 ± 1.6
КИИ2 (n = 20)	3.6 ± 0.03	193.4 ± 1.5

Note: *: p < 0.05 compared with similar indicators in the control group KI1; °: p < 0.05 compared with the control group KI2; &: p < 0.05 compared to the KII1 group; #: p < 0.05 compared to the KII2 group.

In a morphometric study of experimental animals' right and left ventricles and pulmonary arteries, the indicators were higher in group A_3 (Fig. 1). The volume of right ventricle in alloxan-induced diabetes was significantly ($p < 0.05$) greater than in the control groups. In streptozotocin-induced diabetes, these volumetric indicators were 1.17 times higher compared to control groups. The volume of the heart's left ventricle in intact animals was 5.24-5.26 mm^3. In groups A_1, A_2, and A_3, it was significantly ($p < 0.05$) 1.11 times higher; in animals with streptozotocin diabetes, it was 1 times higher. The left ventricle volume was 1.07 times higher than in the control groups. The pulmonary artery in animals with alloxan diabetes increased ($p < 0.05$) by 1.39 times, and in streptozotocin diabetes by 1.35 times compared to control animals. The results of the study of morphometric parameters of cardiomyocytes with alloxan and streptozotocin diabetes at different observation periods are presented in Fig. 2.

The volume fraction of mitochondria in animals of the control groups KI_1, KI_2, and KI_3 were 31.8%, 32.4 and 32.6%, respectively. In contrast, in animals with alloxan diabetes ($p < 0.05$) of groups A_1, A_2, and A_3, these volume rates were the highest (21.8%, 22.4 and 23.8%) than in the streptozotocin and dithizone diabetes. Thus, in streptozotocin-induced diabetes, the volume fraction of mitochondria was 1.52 times less than in the control groups. The capillaries in the myocardium of control animals were 17.1, 17.3, and 17.6 mm^2. In contrast, in animals with alloxan diabetes (A_1, A_2, and A_3), it decreased by 1.15 times and amounted to 10.5, 13,4, and 15.2 mm^2; in animals of C_1, C_2, and C_3 groups, the number of capillaries decreased by 1.53 times compared to the control groups. It was found that the diameter of the capillaries of control animals was 66.3, 66.7, and 65.8 μm, and in animals with alloxan diabetes, it decreased by 1.28 times, while with streptozotocin diabetes, by 1.57 times compared to the control animals. The diameter of left ventricular cardiomyocytes decreased in animals with alloxan diabetes by 1.25 times; in groups with streptozotocin diabetes, it decreased ($p < 0.01$) by 1.53 times compared to the control groups. When comparing the diameter of the left ventricular nuclei of control animals (6.94 μm, 6.92, and 6.96 μm) and animals with alloxan diabetes, this indicator decreased by 1.11 times, while with streptozotocin by 1.28 times ($p < 0.01$) compared to the control groups. Indicators of the nuclear-cytoplasmic ratio and stromal-cytoplasmic ratio of the left ventricle were also reduced in streptozotocin-induced diabetes by 1.18 and 1.29 times, respectively, compared to the indicators of the control groups. The diameter of right ventricular cardiomyocytes significantly decreased in animals with alloxan diabetes by 1.06 times, while in the groups with streptozotocin diabetes by 1.14 times compared to control groups (Fig. 2). In a morphometric study, the diameter of the nuclei of the right ventricle decreased by 1.08 times in animals with alloxan diabetes and by 1.34 times in those with streptozotocin diabetes compared to the control groups. Nuclear-cytoplasmic and stromal-cytoplasmic ratios of the pancreas decreased in animals treated with streptozotocin by 1.07 times compared to the indicators in the control groups. The results of a study of the diameter of cardiomyocytes of the interventricular septum established a decrease in animals with alloxan diabetes by 1.11 times; in streptozotocin diabetes, it was reduced by 1.12 times compared to the control groups. When comparing the diameter of the MP nuclei of control animals (5.41 μm, 5.46, and 5.48 μm) and animals with alloxan diabetes, this indicator decreased by 1.05 times, while with streptozotocin diabetes by 1.07 times compared to the control groups. MP nuclear-cytoplasmic ratios

and stromal-cytoplasmic ratios were especially reduced by 1.21 and 1.13 times in animals with streptozotocin-induced diabetes, respectively. In a morphometric study of the volumetric density of the T-system in the myocardium in experimental animals, we found that in alloxan diabetes in group A_1, this value was 0.0192 μm^3; in streptozotocin C_1 it was 0.0191, in the control animals of group KI_1 0.0086 μm^3. This clear quantitative difference in the volumetric density of the T-system in diabetes was reflected in the functional activity of all cellular elements of the myocardium, especially the sarcoplasmic reticulum (Fig. 3).

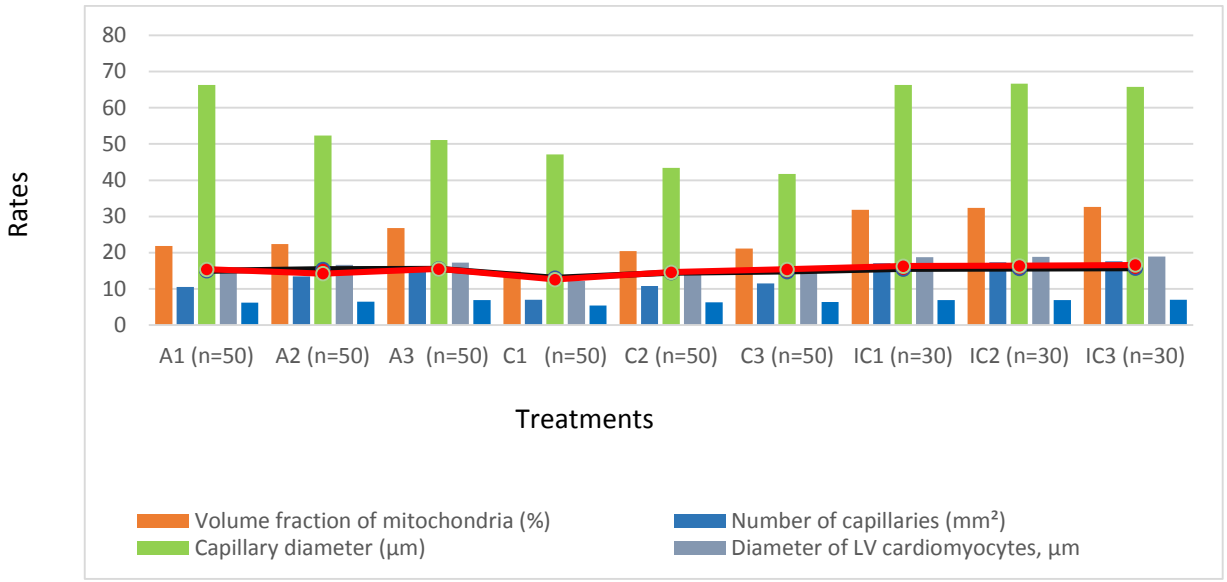

Fig. 1. Morphometric indicators of cardiomyocytes in alloxan- and streptozotocin-induced diabetes at different observation periods.

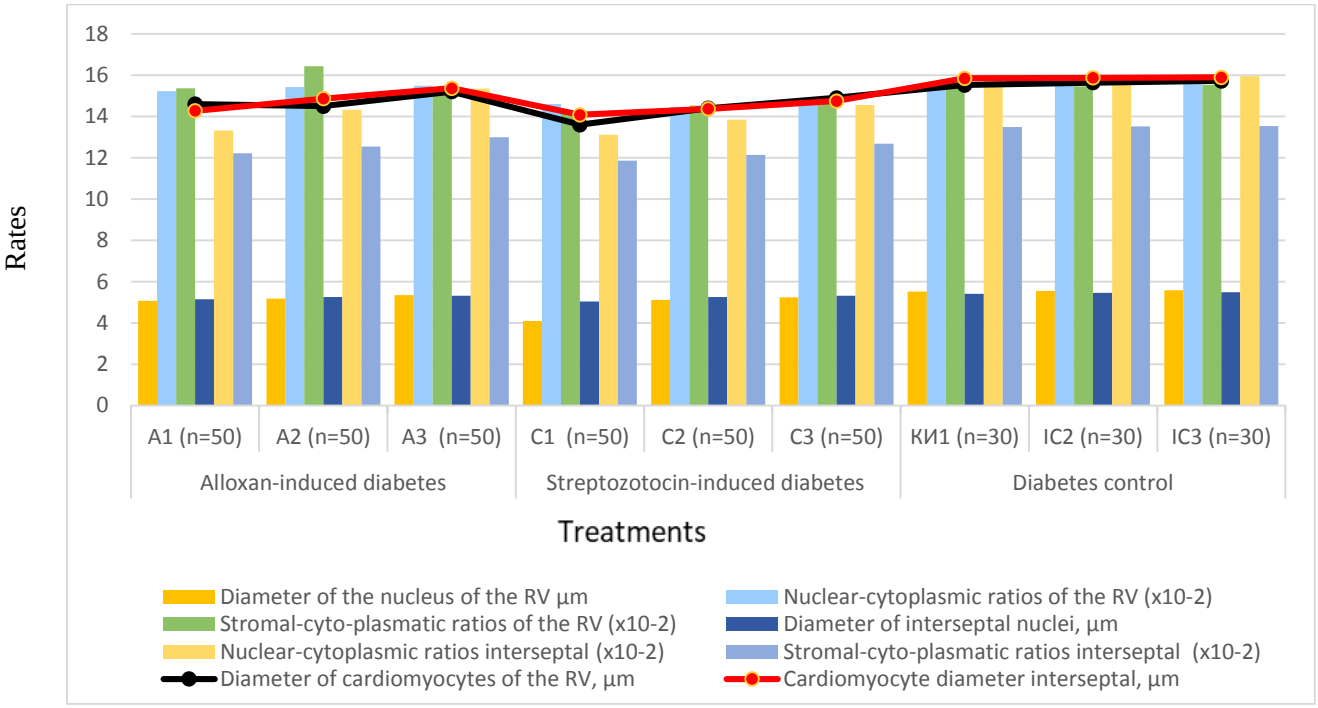

Fig. 2. Morphometric indicators of cardiomyocytes in alloxan- and streptozotocin-induced diabetes at different observation periods.

To determine the quantitative ratio of glycogen granules in experimental animals, we conducted a morphometric study on the volumetric density of glycogen granules in different models of diabetes. In alloxan diabetes in group A_1, this value was 0.1808 μm^3; in streptozotocin diabetes, it was 0.1731, while in intact animals of group KI_1, it was 0.0825 μm^3. From the data presented in Fig. 3, a sharp decrease in the number of capillaries in the myocardium of the left ventricle per unit area was visible: 2104. In the myocardium of the left ventricle with alloxan diabetes,

the indicator was the highest: 1255, while with streptozotocin diabetes, it was1105. These comparisons clearly show the quantitative vascular support of the LV myocardium in experimental diabetes. Cardiomyocytes have tubular invaginations of the sarcolemma at the level of Z-disks, oriented perpendicular to the axis of the myocyte and myofibrils (T-system channels).

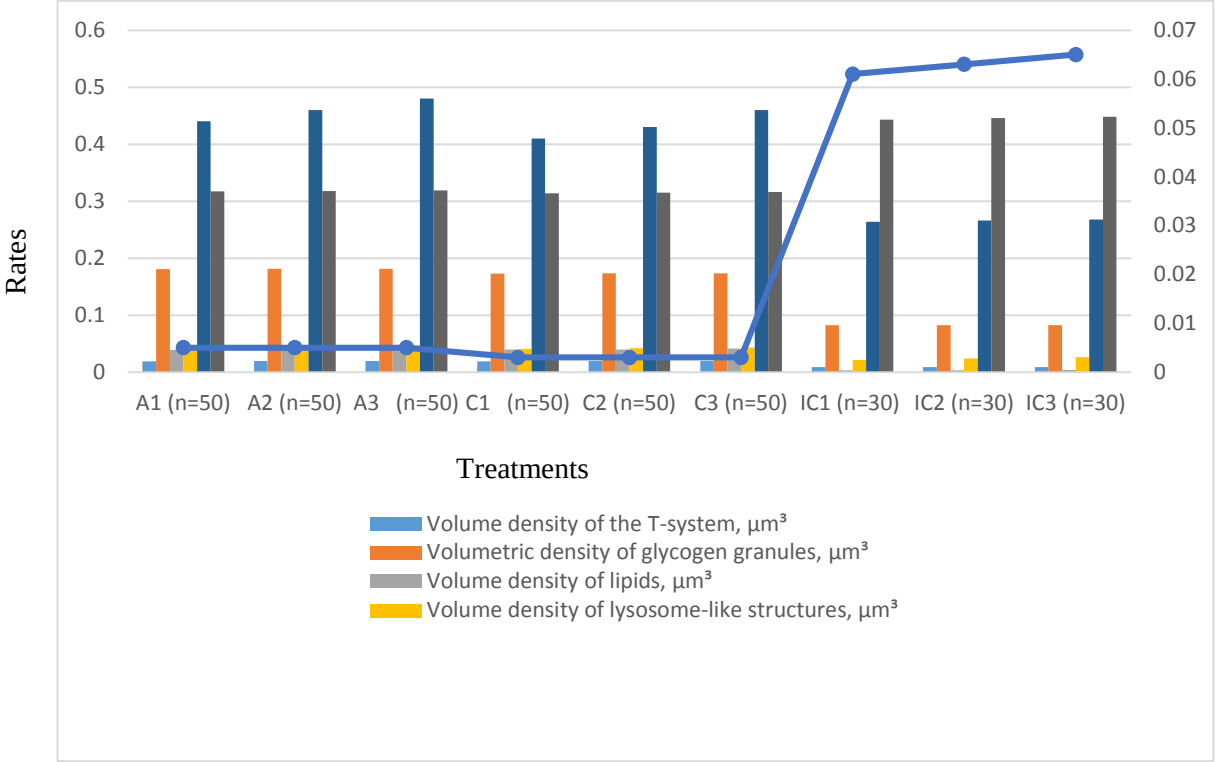

Fig. 3. Morphometric indicators of the volume of heart ventricles and pulmonary artery in animals with experimental diabetes.

Their diameter reaches 150-200 nm. The glycoprotein layer of the sarcolemma extends deep into the channels of the T-system. In a morphometric study of these indicators, we found that the volumetric density of the intermyofibrillar space in experimental animals was significantly higher (0.667 μm^3) than in the control group (0.488 μm^3). Lipid inclusions in the myocardium in experimental animals are caused by impaired carbohydrate metabolism in this disease, so we conducted a morphometric study of the volumetric density of lipids in the myocardium. It was found that in the control group, the volume density of lipids was 0.0038 μm^3, and in alloxan diabetes, it was 0.0394 μm^3. A sharp increase in lipid components in the myocardium during streptozotocin diabetes indicates a metabolic disorder of carbohydrate and lipid metabolism in this disease. Summarizing the data on the study of the myocardium in experimental animals, special attention should be paid to the results of the morphometric study, which most objectively reflect the specifics of changes in the myocardium in diabetes mellitus (Bolaffi *et al*. 1987; Elsner *et al*. 2000; Jaynthi *et al.* 2012; Dreval *et al.* 2014; Radenković *et al*. 2016; Sanchez-Rangel *et al.* 2017; Khandekar *et al.* 2017; Zvenigorodskaya *et al*. 2021; Vasantha *et al*. 2024; Choudhari *et al*. 2024). Analyzing the morphometric data, the following conclusions can be drawn: the volumetric density of cardiomyocytes in different models of diabetes significantly decreased simultaneously with an elevation in the volumetric density of interstitial tissue. At the same time, the diameter and area of cardiomyocytes were significantly higher; in alloxan diabetes, the nuclear area increased, while the nuclear-sarcoplasmic ratio decreased (Zvenigorodskaya *et al*. 2021; Choudhari *et al*. 2024). Reliable quantitative changes were also determined inside cardiomyocytes, affecting almost all organelles and inclusions of the cell. In almost all experimental animals, compared to the control groups, the volume density of mitochondria increased, with a significant drop in the volume density of the contractile structures of cardiomyocytes: myofibrils, which could not but affect the contractility of cardiomyocytes. The volume density of lipid inclusions increased 10 times, the volume density of lysosome-like formations reliably increased almost 2 times, and the volume density of the T-system in diabetes increased 2 times, indicating a significant ruggedness of cardiomyocytes and was a compensatory-adaptive reaction cell, since by a sharply increased diameter and area of cardiomyocytes, the conduction of impulses to the

sarcoplasmic reticulum and myofibrils is difficult. The same applies to delivering metabolic substrates and oxygen to the cardiomyocyte. In alloxan diabetes, the volumetric density of the intermyofirillary space increased. We can explain this fact by a sharply elevated number of glycogen granules accumulating in cardiomyocytes and a drop in the volumetric density of myofibrils. All these changes in experimental diabetes are most likely due to a sharp decrease in the number of microvessels: capillaries that deliver substrates for metabolism and oxygen to cardiomyocytes. Moreover, their density was significantly lower in the experimental group of diseased animals compared to the indicators in control rats. Thus, cardiac hypertrophy is associated with a more rapid elevation in the number of myocytes compared to the expansion rate of the vascular network, which leads to a relative decrease in the network density of coronary arterioles and capillaries. As a result of the rarefaction of the capillary network, the distance over which diffusion of nutrient substrates occurs increases, the density of the network of arterioles drops, and vascular resistance upraises. The thickness of the arteriolar wall and its ratio to the lumen of the vessel also increases. We believe that metabolic disorders associated with the delivery and utilization of energy substrates by the myocardium may play a decisive role in the development of diabetic cardiomyopathy.

CONCLUSION

1. In a morphometric study of experimental animals' right, left ventricle, and pulmonary arteries, the indicators were higher in group A_3 after 24 months of observation. The volume of the heart's right ventricle in alloxan-induced diabetes was significantly ($p < 0.05$) greater than in the control groups.
2. Morphometric parameters of the heart of rats with streptozotocin diabetes; cardiomyocytes were distinguished by pronounced ultrastructural changes: lysis of cristae and outer mitochondrial membranes with the formation of myelin figures and dense protein bodies.
3. For alloxan diabetes after 24 months, processes of hypertrophy of cardiomyocytes prevailed: nuclei volume increased ($p < 0.05$) by 34.6%, and euchromatin content and mitochondria by 23.8%.

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