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# CRITERIA FOR ASSESSING STRUCTURAL CHANGES IN THE MYOCARDIUM IN EXPERIMENTAL HYPODYNAMIC AND DIABETES

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## ABSTRACT

The study is devoted to morphological changes in the myocardium under conditions of hypodynamia and diabetes mellitus, which are currently an urgent problem. The study examined heart tissue from 120 rats exposed to hypodynamia and diabetes mellitus and their offspring. The results showed that dystrophic changes are observed in the heart walls of rats under conditions of diabetes mellitus. The maximum level of the inflammatory process was noted in our observations. During this period, perivascular hemorrhages, interstitial edema, lymphohistiocytic infiltration, as well as signs of mucoid and fibrinoid thickening in the myocardial stroma, are observed. Inflammatory processes are more pronounced in the subendocardial area, and an increase in edema is detected.

**Key words:** diabetes, hypodynamia, myocardium, heart, white laboratory rats.

## INTRODUCTION

The study of the human heart has been relevant for many years. Modern literature contains a wealth of scientific information about the anatomy, physiology, and embryology of the heart, as well as their changes with age. Today, mortality and disability from cardiovascular diseases occupy a high rank among the population. The rapid development of cardiology and cardiac surgery requires a comprehensive study of the heart and its changes with age [1, 5, 7, 9, 15]. Acceleration and changes in anthropometric dimensions from year to year lead to

an increased demand for studying the anatomical structure of organs and systems and changes in their indicators [2, 6, 11, 14].

According to the World Health Organization, cardiovascular diseases are one of the leading causes of death worldwide. In 2016, 17.9 million people died from cardiovascular diseases, accounting for 44% of all deaths from non-communicable diseases worldwide [World Health Organization, 2016].

Every year, the incidence of cardiovascular diseases in our Republic is steadily increasing and affecting younger populations. According to scientific literature, 20–25% of the elderly population has hypertension, 11% has ischemic heart disease, and 1% has experienced a myocardial infarction [3, 8, 10, 13]. According to the State Statistics Committee for 2019, the mortality rate from cardiovascular diseases in Uzbekistan exceeds 62.1%, and the share of disability is more than 25% [State Statistics Committee of Uzbekistan, 2019].

Diabetes mellitus is a disease that causes early disability and high mortality, primarily due to cardiovascular diseases. In 2000, 175.4 million people worldwide had diabetes (2.07 million of them in Russia), and by 2025, their number is expected to reach 380 million (4.51 million in Russia). According to diabetologist Joslin, 50.2% of deaths in people with diabetes are due to coronary artery disease, 12.1% to cerebrovascular disease, 11.3% to renal artery disease, and 2.3% to peripheral artery disease [4, 12, 16, 17]. Diabetes mellitus is a life-threatening factor for patients with cardiovascular diseases. Cardiovascular complications of diabetes account for 60% of deaths. The risk of developing cardiovascular disease in people with diabetes is 2–4 times higher than in the general population.

Based on the above, it can be said that the topic is dedicated to a pressing problem in medicine today. The author set the goal of studying the morphological and morphometric changes of the myocardium in experimental hypodynamia and diabetes mellitus in a growing organism.

## Purpose of the Research

The main objective of this study is to analyze morphological and morphometric changes in the myocardial layer of white laboratory rats at different stages of ontogenesis under conditions of experimental hypodynamia and diabetes mellitus.

## Materials and Methods

To achieve the study's objectives, 100 nulliparous, non-bred female white rats weighing 160–180 grams were used, along with a total of 220 rat pups (100 in the

control group and 120 in the experimental group). All experimental animals were maintained on a standard laboratory diet.

The female rats were divided into two groups. The first group consisted of intact adult rats, serving as the control group. In the second group, rats were placed in specialized cages to induce experimental hypodynamia, and experimental diabetes was induced by intraperitoneal injection of 4 mg of streptozotocin per 100 g of body weight. Blood glucose levels were measured daily by collecting blood from the tail vein. Subsequently, the second phase of the experiment was conducted: female rats were mated with healthy male rats, and pregnancy was monitored. Pregnancy was confirmed by the presence of spermatozoa in vaginal smears. Once pregnant, female rats were separated from males and housed in individual cages.

A total of 120 rat pups were born to female rats with experimental hypodynamia and diabetes, while 100 rat pups were born to intact female rats. The offspring from both groups were examined on days 7, 14, 21, 30, and 60 of postnatal ontogenesis. For the first month after birth, rat pups were kept with their mothers, after which they were separated by sex and housed in individual cages. The experimental group consisted of 120 rat pups born to mothers with hypodynamia and diabetes, while the control group included 100 rat pups born to intact mothers.

The rat pups were euthanized by decapitation on days 7, 14, 21, 30, and 60 after birth. Heart tissue was excised for histological examination. To isolate cardiomyocytes from heart tissue, the alkaline tissue dissociation method developed by V. Ya. Brodsky et al. (1983) was employed. Myocardial sections from the atria and ventricles were fixed in cold 10% neutral formalin in phosphate buffer (pH 7.0) for 10–14 days. Subsequently, 1–2 mm cross-sections were prepared from the tissue and immersed in 50% potassium carbonate for two days. Blood was carefully removed using a pipette, and the tissue sections were placed in distilled water for 1–2 days in a refrigerator. After two hours at room temperature, the water was gradually removed, and freshly distilled water was added at a rate of 1 ml per 2 mg of myocardium. The final separation of cardiomyocytes was performed using a magnetic stirrer for 20–30 minutes. The quality of cardiomyocyte separation was assessed by visual inspection of the suspension. The resulting suspension was placed on a slide, air-dried at room temperature, and stained with hematoxylin and eosin using standard methods.

Experiments and euthanasia by decapitation were conducted in accordance with the “European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes” (Strasbourg, 1986). Histological

sections, prepared using a rotary microtome to a thickness of 8–10 microns, were stained with hematoxylin and eosin according to the standard method (Volkova O. V. and Yeletsky Yu. K., 1982).

**Results**

The rat heart is anatomically similar to the human heart but has its own unique features. Since rats are small laboratory animals, their hearts are significantly smaller. The rat heart is located in the chest cavity, between the lungs and diaphragm, protected by the ribs (see Figure 1). The heart is small, making up about 0.3–0.5% of the rat's body mass. The rat heart, like the human heart, has four chambers and four main valves. The heart is a muscular organ and the main organ of the circulatory system that moves blood. The heart wall consists of three layers: the inner endocardium, the middle myocardium, and the outer epicardium (see Figure 2). The heart is surrounded by a connective tissue membrane—the pericardium, i.e., the pericardial sac. The myocardium is the most developed and most important layer of the heart. The myocardium is composed of striated muscle tissue, in which typical and atypical muscle fibers are distinguished. Typical muscle fibers perform the function of contraction, while atypical fibers conduct excitation.

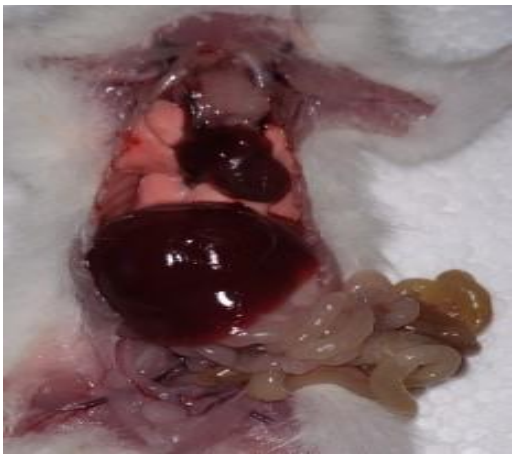


**Figure 1.** Location of the rat heart in the chest.

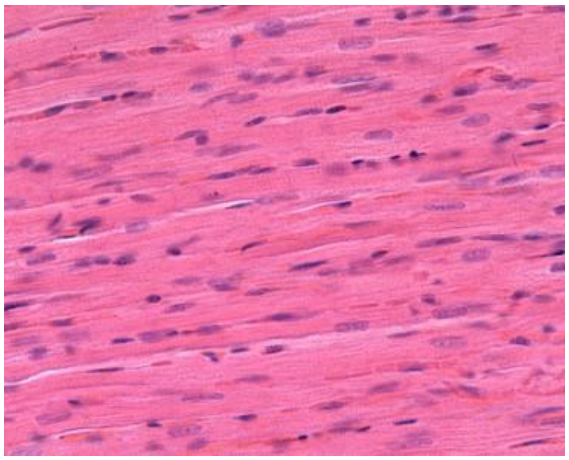
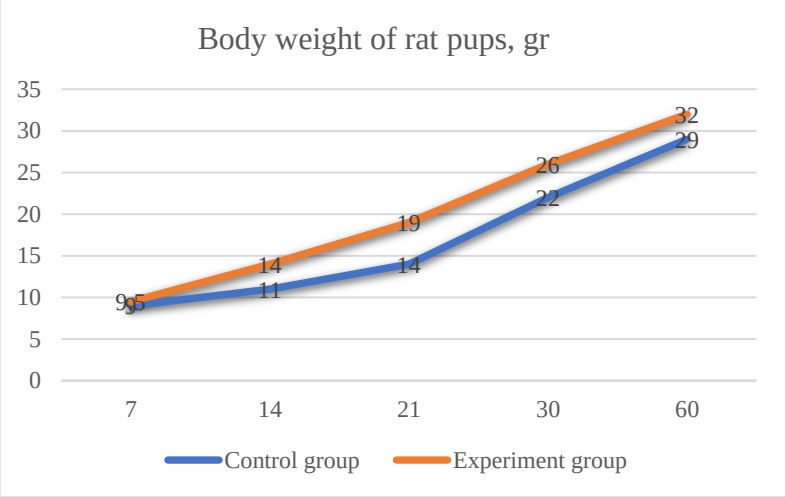


**Figure 2.** View of the myocardial layer of the 21-day control rat heart. Stained with hematoxylin and eosin. X: 10x40.

Typical muscle fibers are composed of individual contractile muscle cells—cardiomyocytes. Cardiomyocytes differ from atypical muscle cells and skeletal striated muscle fibers in several structural and cytochemical features. These cells are arranged in a row, forming a muscle fiber. Muscle fibers are divided into individual segments—cell bundles—by means of intercalated discs. Their structure is considered in the section on general histology, muscle tissue, and cardiac muscle

tissue. The shape of contractile muscle cells of the heart can be compared to a cylinder. Their length reaches 50–100 μm, and their diameter reaches 17–20 μm. In the central part of cardiomyocytes, an oval-shaped nucleus is located. The heart muscle is covered with a sarcolemma. An electron microscope has revealed that the sarcolemma consists of an inner plasmolemma and an outer basal membrane. The sarcolemma participates in the formation of intercalated discs. The intercalated discs run transversely to the muscle fiber and appear as dark streaks in conventional preparations. They are the most characteristic structures of the heart muscle. The intercalated discs are the intermyocyte boundaries formed by the plasma membranes of two adjacent cells, separated by a narrow intercellular space. The sarcoplasm of cardiomyocytes contains general and special organelles of the cell. Special organelles—myofibrils—are the most important structures of muscle cells, performing the function of contraction. The myofibrils of cardiomyocytes do not differ in structure from the myofibrils of skeletal striated muscle. In the longitudinal section of muscle fibers, the transverse view of the myofibrils is visible. An electron microscope shows that myofibrils consist of very thin myofilaments (protofibrils). Another important organelle of cardiomyocytes is the smooth endoplasmic reticulum (sarcoplasmic reticulum), which consists of a system of longitudinal and transverse tubes. Typical cardiac muscle is rich in mitochondria. They are elongated, oval in shape, and lie between the myofibrils. Sometimes clusters of mitochondria can be seen near the nucleus. Mitochondria are also densely attached to myofibrils under the sarcolemma, near the capillaries. Mitochondria have a large number of densely packed cristae. The Golgi complex and the rough endoplasmic reticulum are poorly developed. In the myocardium of rats, cardiomyocytes are arranged in the form of densely packed parallel bundles or bundles of different directions. Each cardiomyocyte has one or two elongated oval-shaped nuclei, which are located in the center and are surrounded by strictly linear myofibrils along the periphery. The area of the compartmental cardiomyocytes is smaller and more freely located. The myocardium of rats mainly consists of binucleated cardiomyocytes.

The rat heart is located asymmetrically in the chest and occupies a large area on the left side. With an increase in body weight, the absolute weight of the heart increases significantly. The highest rate of rat weight gain occurs on the 21st day (50%). From birth to 21 days of age, the weight of the rat increases threefold, and the heart weight increases 1.7 times. In newborn rats, the heart weight is 1.75% of the body weight. With increasing age, the relative weight of the heart decreases relative to body weight and is 1.1% on the 21st day of postnatal ontogenesis (see Diagram 1).




Since all anatomical parameters in newborn rats are almost the same, in most cases, their heart has a spherical shape. During postnatal ontogenesis, the growth of the length, width, and anterior-posterior dimensions of the heart does not occur uniformly. Starting from the 14th day, the length of the heart grows faster than its width and anterior-posterior dimensions, as a result of which the shape of the heart becomes elongated. The highest growth rate of anatomical parameters was observed in 14-day-old rats, while in 30-day-old rats, the increase in the anterior-posterior dimensions of the heart resulted in its conical shape. It was found that all dimensions of the hearts of the rats in the experimental group were larger than those of the control group.

In experimental hypodynamia and diabetes mellitus, intracellular and intercellular edema were detected in the myocardium. The cytoplasm of damaged cardiomyocytes was vacuolated. Polymorphism of isolated cardiomyocytes was detected. Gradual disappearance of tumors was observed, and transverse proliferation was clearly reflected in these cardiomyocytes. Most cardiomyocytes are binucleated. When studying the morphometric parameters of isolated cardiomyocytes, it was found that the cardiomyocytes of the right ventricle increased by an average of 11.65±0.29 μm compared to the control group. At the same time, the size of the cardiomyocytes of the right ventricle was also observed to increase correspondingly. The nuclei of the myocardial cells of the rats in the experimental group were observed to be smaller. We associate this phenomenon with the fact that more secretory cells are located in the right ventricle of the heart.

On the 7th day of the experiment, the histological appearance of the myocardium did not differ from the control group. Cardiomyocytes form elongated muscle fibers. The nuclei of oval-shaped cardiomyocytes are located in the center of the fiber, and myofibrils are clearly distinguished. The average length of left ventricular cardiomyocytes in the 7-day experimental group was 97.44±3.61 μm,

and the length of right ventricular cardiomyocytes was 111.17±4.2 μm. The length of right ventricular cardiomyocytes increased by 9% compared to left ventricular cardiomyocytes ($p<0.05$). The average size of left ventricular cardiomyocyte nuclei in the 7-day experimental group was 5.21±0.22 μm, and the size of right ventricular cardiomyocyte nuclei was 5.61±0.16 μm. The size of the right ventricular cardiomyocyte nuclei increased by 6% compared to the left ventricular cardiomyocyte nuclei ($p<0.05$).

On the 14th day of the experiment, the wall thickness of all sections of the heart was smaller than in the control group. Blood filling, stasis, and diapedesis hemorrhages were detected in the small vessels of the heart, accompanied by perivascular edema, swelling, and disorganization of the connective tissue stroma. The presence of dilated and fully flowing vessels was detected in the subepicardial zone of the myocardium. Mild edema was detected in the myocardial stroma, mainly around the vessels. In some cardiomyocytes, intracellular edema was detected in the form of accumulation of vacuoles filled with tissue fluid in the cytoplasm and interstitial edema (see Fig. 3). The average length of left ventricular cardiomyocytes in the 14-day experimental group was 105.32±4.05 μm, and the length of right ventricular cardiomyocytes was 121.24±5.05 μm. The length of right ventricular cardiomyocytes increased by 12% compared to left ventricular cardiomyocytes ($p<0.05$). The average size of left ventricular cardiomyocyte nuclei in the 14-day experimental group was 5.86±0.3 μm, and the size of right ventricular cardiomyocyte nuclei was 6.92±0.36 μm. The size of right ventricular cardiomyocyte nuclei increased by 8% compared to left ventricular cardiomyocyte nuclei ($p<0.05$).

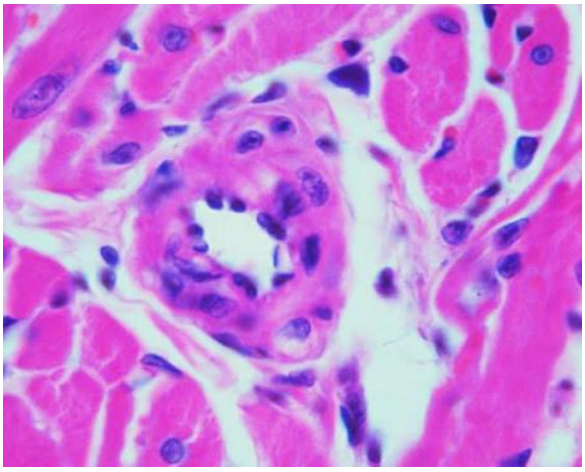


**Figure 3.** Rat myocardium on day 14 of the experiment. Interstitial edema of the myocardium. Stained with hematoxylin and eosin. X: 10x40.

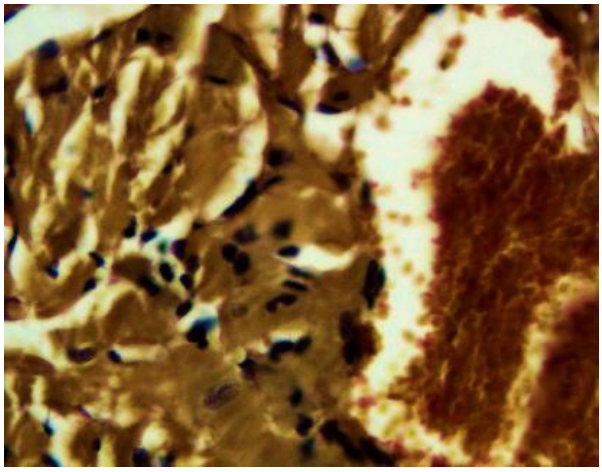


**Figure 4.** Rat myocardium on day 30 of the experiment. Perivascular hemorrhages in the form of diapedesis between myocardial tissue. Stained with Van Gieson's.

After 21 days of the experiment, an increase in edema was observed in the myocardial stroma, mainly in the perivenular and pericapillary spaces. In the areas of edema, swelling of collagen fibers and their homogenization occurred, and superficial disorganization of connective tissue with the accumulation of glycosaminoglycans was detected. The blood vessels have a rounded shape due to endothelial cell edema. The appearance of small vacuoles containing clear cytoplasmic fluid in the cytoplasm of cardiomyocytes was observed, indicating the development of hydropic dystrophy in cardiomyocytes. Intracellular edema was focal, and both cardiomyocytes with dystrophic changes and unchanged cardiomyocytes could be seen. The average length of left ventricular cardiomyocytes in the 21-day experimental group was 115.52±4.7 μm, and the length of right ventricular cardiomyocytes was 132.1±5.6 μm. The length of right ventricular cardiomyocytes increased by 14% compared to left ventricular cardiomyocytes ($p<0.05$). The average size of left ventricular cardiomyocyte nuclei in the 21-day experimental group was 6.15±0.41 μm, and the size of right ventricular cardiomyocyte nuclei was 7.42±0.48 μm. The size of right ventricular cardiomyocyte nuclei increased by 10% compared to left ventricular cardiomyocyte nuclei ($p<0.05$).

On the 30th day of the experiment, changes in the myocardial blood vessels persisted, i.e., venous engorgement, blood stagnation, and perivascular hemorrhages in the form of numerous diapedesis were noted (see Fig. 4). Intramuscular fluid was observed to cause muscle fiber displacement. Initially focal, then diffuse infiltrates consisting of lymphocytes, histiocytes, and fibroblasts were observed in the myocardial tissue. Signs of mucoid and fibrinoid thickening were detected in the myocardial stroma. Signs of protein hydropic dystrophy were observed in cardiomyocytes, intracellular edema appeared, and numerous foci of plasmolysis were detected in the myocardium. The average length of left ventricular cardiomyocytes in the 30-day experimental group was 120.31±4.97 μm, and the length of right ventricular cardiomyocytes was 138.6±5.9 μm. The length of right ventricular cardiomyocytes increased by 17% compared to left ventricular cardiomyocytes ($p<0.05$). The average size of left ventricular cardiomyocyte nuclei in the 30-day experimental group was 6.5±0.52 μm, and the size of right ventricular cardiomyocyte nuclei was 7.91±0.56 μm. The size of right ventricular cardiomyocyte nuclei increased by 13% compared to left ventricular cardiomyocyte nuclei ($p<0.05$).

On the 60th day of the experiment, interstitial edema increased and spread throughout the myocardium. The edema led to the swelling of collagen fibers and their disruption. The myocardial tissue thickened, and disorganization of the

surrounding connective tissue fibers was observed. Dystrophic changes in the myocardium were diffuse in nature, and along with interstitial edema, intracellular edema, and myocytolysis, there was an increase in reparative processes, which was manifested not only by the intensive proliferation of fibroblasts around the vessels but also in the intermuscular tissue. Disruption of muscle fibers and focal edema were detected. More pronounced edema was observed in the subendocardial area of the myocardium. The average length of left ventricular cardiomyocytes in the 60-day experimental group was 125.65±5.61 μm, and the length of right ventricular cardiomyocytes was 141.15±6.3 μm. The length of right ventricular cardiomyocytes increased by 19% compared to left ventricular cardiomyocytes ($p<0.05$). The average size of left ventricular cardiomyocyte nuclei in the 60-day experimental group was 6.84±0.64 μm, and the size of right ventricular cardiomyocyte nuclei was 8.21±0.61 μm. The size of right ventricular cardiomyocyte nuclei increased by 5% compared to left ventricular cardiomyocyte nuclei ($p<0.05$).

**Discussion**

Thus, it was found that the body weight and heart weight of the rat pups in the experimental group were greater than those in the control group. The results of our studies showed that a significant increase in body weight and heart weight was detected at 14 days. Compared with the control group, the body weight was 35% greater, and the heart weight was 19% greater.

On days 21–30 of the experiment, edema increased in the perivenular and pericapillary spaces. It was found that collagen fibers swelled, and signs of superficial disorganization of the connective tissue began to appear. The endothelial cells of the blood vessels had a rounded shape due to edema. In cardiomyocytes, a clear cytoplasmic fluid appeared in the cytoplasm of small vacuoles, leading to the development of hydropic dystrophy in cardiomyocytes. Cellular edema was found to be focal on day 21 of the experiment, and by day 30, it was found to be diffuse. It was observed that the fluid between cardiomyocytes caused the muscle fibers to slide. Small infiltrates consisting of lymphocytes, histiocytes, and fibroblasts were seen in the myocardial tissue. Signs of protein hydropic dystrophy were observed in cardiomyocytes, and numerous foci of plasmolysis were detected in the myocardium.

On the 60th day of the experiment, interstitial edema increased and spread throughout the myocardium. On this day of the experiment, cardiomyocyte injury was clearly visible. The edema led to the swelling of collagen fibers and the disruption of their fibers. Myocardial tissue thickening and disorganization of the

surrounding connective tissue fibers were detected. Dystrophic changes in the myocardium were diffuse in nature, with increased absorption of the cytoplasm, intracellular edema, and myocytolysis. Disruption of muscle fibers and focal edema were detected.

**Conclusion**

The hearts of the experimental group of young rats showed disorganization of connective tissue in the walls of arterioles and capillaries, as well as changes in myocardial muscle fibers in the form of protein dystrophy and myofibril fibrils, such as pathomorphological changes.

The rat heart is generally similar to the human heart in terms of anatomical structure but has its own characteristics. Since rats are small laboratory animals, their hearts are significantly smaller but have the same histological structure. In the experimental group of young rats, a significant increase in the morphometric parameters of the thickness of the ventricular wall was observed compared to the control group.

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