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ANALYTICAL AND QUANTITATIVE ASSESSMENT OF THE CONDITION OF THE HEART WALL OF RATS EXPOSED TO THE VENOM OF THE VIPERS VIPERA BERUS BERUS AND VIPERA BERUS NIKOLSKII

Bobr A.M. ✉ **Analytical and quantitative assessment of the condition of the heart wall of rats exposed to the venom of the vipers Vipera berus berus and Vipera berus nikolskii.**
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ABSTRACT. Background. A significant number of factors of both physical and chemical origin can have a negative impact on the organs of the cardiovascular system. At the same time, implementing the damaging effect of factors of various genesis consists not only of changes in the normal functioning of the heart but also in the launch of complex pathogenetic mechanisms that cause pronounced structural changes in the organ, which are sometimes irreversible. **Objective.** The aim of the study is an analytical and quantitative assessment of the heart wall of rats exposed to the venom of the vipers Vipera berus berus and Vipera berus nikolskii. **Methods.** Experimental studies were conducted on white nonlinear male rats. The animals were conditionally divided into control and experimental groups, ten individuals each. Experimental rats were intraperitoneally administered a semi-lethal dose (LD_{50}) (1.576 mg· g^{-1}) of the venom of Vipera berus berus and Vipera berus nikolskii in saline. The animals of the control group were intraperitoneally injected with saline only. Rats were removed from the experiment 24 hours after exposure to the poison and anaesthetised by cervical dislocation. Heart samples were taken for microscopic examination. Material fixation and preparation of paraffin blocks were carried out according to generally accepted methods. Histological preparations of the heart were stained with Picro Sirius Red/Fast Green and hematoxylin-eosin. For a detailed assessment of the effect of the venom of two species of vipers on the general condition of the rat heart, we compared absolute and relative variables, which were measured and calculated, respectively, using Fiji: ImageJ program, between the control and both experimental groups exposed to the venom of the vipers Vipera berus berus and Vipera berus nikolskii. Statistical processing was carried out using the Excel program with subsequent construction of graphs to visualise the results obtained. **Results and conclusion.** According to the data of morphometric studies, a more pronounced harmful effect of the venom of Vipera berus nikolskii was established, which was manifested in the violation of the structure and shape, oedema of cardiomyocytes, which led to significantly higher indicators of the width of these cells both in comparison with the control group and with the second experimental group. In addition, the action of both venoms, albeit to different degrees, led to the growth of connective tissue elements within the endomysium, which was reflected in an increase in the indicator of the proportion of this tissue in the myocardium. The venoms of both vipers provoked an increase in the proportion of connective tissue in the myocardium; however, against the background of oedema of muscle cells, the relative increase in the area of endomysium to them shows a tendency to increase but is not reliable.
Key words: vipers, venom, heart, sarcoplasm, muscle fibres, rats.

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Introduction

A significant number of factors of both physical and chemical origin can have a negative impact on the organs of the cardiovascular system. At the same time, the implementation of the damaging effect of factors of various genesis consists not only of changes in the normal functioning of the heart but also in the launch of complex pathogenetic mechanisms that cause pronounced structural changes in the organ, which are sometimes irreversible [1, 2]. That is why a comprehensive study and generalisation of the features and pathways of damage to the cardiovascular system is critical.

Cardiotoxicity and pronounced electrocardiographic changes are frequent complications of snake bites [3, 4, 5]. The most common are sinus arrhythmia, atrioventricular block and sinus bradycardia. Cases of snake bites of the Viperidae family are often associated with pathologies such as myocardial infarction and ischemic stroke, which arise as a result of activation of the coagulation cascade of blood coagulation and direct cardiotoxicity of proteolytic enzymes of the venom, in particular SVMP (snake venom metalloproteinases). Also, their toxins' components cause hypofibrinogenemia, damage to the vascular endothelium and impaired platelet aggregation [6, 7, 8, 9]. According to the literature, the pathogenesis of myocardial infarction in the bites of snakes of the Viperidae family also includes impaired oxygen supply to cardiomyocytes due to excessive hemolysis of erythrocytes, vasoconstriction of coronary vessels due to significant production of endothelin and the effect of aflatoxins of the venom. Scientists note that the development of myocarditis with pronounced necrosis of contractile myocytes, haemorrhages and accumulation of blood clots in the vessels of the microcirculatory bed of the heart muscle is possible [10, 11, 12].

Cobra cardiotoxins cause impaired contractility, depolarisation and contracture of the heart muscle. It has been established that when they affect the papillary muscle of the heart of guinea pigs, they exhibit a transient positive inotropic effect accompanied by the development of tonic contraction. Studies of the mechanisms of action of cobra cardiotoxin show that in cardiomyocytes, they cause an increase in Ca^{2+} ions, a change in their shape, hypercontracture, and destruction of the plasmalemma. The latter fact is associated with the ability of cardiotoxin to interact with cell membrane lipids. At the same time, the characteristic features of this interaction depend on the type of toxin – P or S. The P-type contains proline at position 30 of the amino acid sequence; the S-type contains a serine residue at position 28. There is evidence that both types cause destabilisation of the lipid bilayer of cardiomyocyte cell membranes but with different intensities [13, 14]. The features of the cardiotoxic effect of snake venom, especially of the Viperidae family, on the heart muscle's structural organisation and functional properties have not yet been elucidated. Experimental data available in scientometric databases are few and do not fully reveal the picture of pathological changes. Since the problem of snake bites is steadily growing every year worldwide, studying the effect of viper venom toxins on the organs of the cardiovascular system is an important task today.

The study aims to analytically and quantitatively assess the condition of the heart wall of rats exposed to the venom of the vipers Vipera berus berus and Vipera berus nikolskii.

Materials and methods

Experimental studies were conducted on white, non-linear male rats. For preliminary acclimatisation, the animals were kept in the Taras Shevchenko National University of Kyiv animal facility for 7 days and then in laboratory conditions in compliance with temperature and light regimes. Rats received standard food and water ad libitum. All experiments were conducted following the Recommendations of the National Institute of Health for the Care and Use of Laboratory Animals and the European Council Directive of November 24, 1986 on the Care and Use of Laboratory Animals (86/609/EEC). The studies were approved and confirmed by the Bioethics Commission of the National Scientific Center "Institute of Biology and Medicine" of Taras Shevchenko National University of Kyiv (protocol No. 2 dated 08/19/2021). Viper venom Vipera berus berus and Vipera berus nikolskii were obtained from V. N. Karazin Kharkiv National University. Lyophilised native venom was stored at -20°C and dissolved in saline immediately before the experiment.

The animals were conditionally divided into control and experimental groups of ten individuals. In saline, experimental rats were intraperitoneally injected with a semi-lethal dose (LD_{50}) (1.576 mg· g-1) of Vipera berus berus and Vipera berus nikolskii venom. Animals in the control group were intraperitoneally injected with saline only. Rats were removed from the experiment 24 hours after exposure to the venom and euthanised by cervical dislocation.

For a detailed assessment of the effect of the venom of two species of vipers on the general condition of the rat heart, we compared absolute and relative variables, which were measured and calculated, respectively, using Fiji: ImageJ program, between the control and both experimental groups exposed to the venom of the vipers Vipera berus berus and Vipera berus nikolskii.

The width of cardiomyocytes in the myocardium was measured. To increase the accuracy of the measurements, the width of heart muscle cells was estimated at a magnification of x1000 on digital images of preparations stained with eosin and hematoxylin. The width of the fibres was measured in microns and compared between three groups of rats. In each, the width of 4 random fibres was measured in 20 different “fields of view” - digital images taken in other parts of the organ. Thus, we had 80 measurements for the control and both experimental groups.

When photographing, a 0.01 mm scale was applied to the image to correctly establish the relationship between the points of the digital image and the micrometres.

The second parameter we chose for quantitative assessment and analytical analysis was the ratio of the area of the endomysium present between the myocardial fibres to the area of the fibres themselves. To perform these measurements, we used digital images of preparations stained using the Picrosirius Red method, which leads to the colouring of collagen fibres in red and cardiomyocytes in green. This creates a colour contrast sufficient for applying thresholds in Fiji: ImageJ program, filtering out one colour using these thresholds and measuring the area occupied by the other. Measurements were performed on images of preparations taken at a magnification of x1000.

We measured the area of the endomysium in μm^2. We calculated the percentage of the area occupied by the connective tissue element relative to the entire preparation area using Fiji: ImageJ program.

Statistical processing was carried out in Excel with subsequent construction of graphs to visualise the results.

Results and conclusion

Since when checking the measurements from the control and both experimental groups for normal distribution, the graphs did not correspond to a Gaussian curve; we used the nonparametric Mann-Whitney test to determine the significance of the differences between the groups.

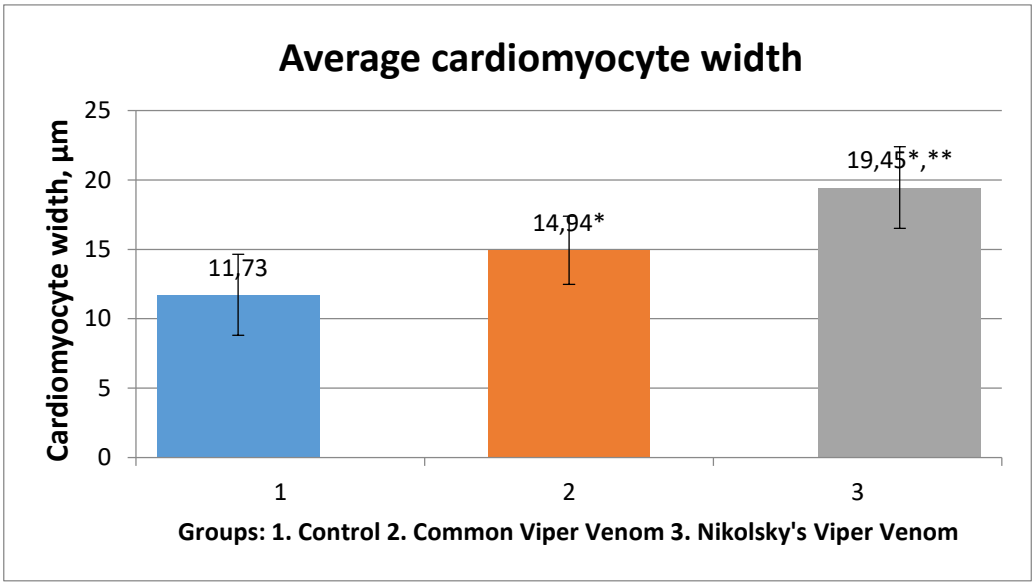

Fig. 1. The average value of the width of cardiomyocytes in the control group, the group introducing Vipera berus berus venom and Vipera berus nikolskii. * - The difference from the control group is significant at p≤0.05, ** - the difference from the group with the introduction of Vipera berus berus venom is significant at p≤0.05.

According to our measurements, a significant difference in the width of cardiac muscle cells was found not only between the control group and rats from the groups exposed to the venom of both species of vipers (Vipera berus berus and Vipera berus nikolskii) but also between these two experimental groups (Fig. 1).

If the average value of this indicator for the control group is 11.72985 µm (first quartile 9.76525 µm; third quartile 12.6685 µm), then for the group whose animals were exposed to the venom of Vipera berus berus, it is 14.93661 µm (first quartile 13.07675 µm; third quartile 16.49025 µm). A significant expansion of cardiomyocytes in this experimental group relative to the control is a logical consequence of the venom's effect on the heart's structures. It is fully correlated with morphological changes in this organ.

When describing the condition of the heart of animals from the experimental group exposed to the venom of the Common Viper, oedema was observed in the muscle fibres, which was probably caused by vacuolisation of the sarcoplasm. The effect of toxic substances causes microcirculation disorders already 3 hours after the external poisonous effect on the organ, which, in turn, leads to acute myocardial hypoxia, which is morphologically expressed in vacuolisation of the sarcoplasm, probably due to the expansion of the internal lumen of the smooth endoplasmic reticulum and oedema of lysosomes in an attempt to fight toxins that have entered the cell cytoplasm. In addition, we noted a violation of the shape of cardiomyocytes, which could not be reflected in their diameter. If in the control group, cardiomyocytes were characterised by clear boundaries and a regular rectangular shape, under the influence of the venom, a loss of the rectangular shape, irregularity and roundness, and convexity of the contours were noted. Such changes in cell shape are quantitatively reflected in increased width.

In addition, during the morphological description of cardiomyocytes, a violation of myocardial striation was noticeable, which indicates a violation in the cytoplasm associated with the regular and clear organisation of actin and myosin fibres - the stratification of these structures also increases the volume of the cytoplasm, and, accordingly, the width of the cell.

If we talk about the surface complex of cells, then the morphological study showed local areas of destruction of the sarcolemma, which is an essential factor in limiting and structuring the cytoplasm. When the structure of the sarcolemma, the precise organisation of actin and myosin fibres, is disturbed, the sarcoplasmic reticulum cisterns likely expand; all these factors together affect the increase in the size of cardiomyocytes, which is reflected in the results of our measurements.

Pronounced pathological changes in the heart wall of rats from the experimental group exposed to the venom of the viper Vipera berus nikolskii are reflected in both the results of morphological and morphometric studies (Fig. 1). The average width of cardiomyocytes of animals exposed to the venom of this species of a viper is 19.45278 μm (first quartile 17.18925 μm; third quartile 21.22775 μm) - significantly greater not only than the parameters of the control group but also statistically significantly different from the width of these cells in animals from the group exposed to the venom of the common viper. This indicates a powerfully destructive effect of the studied venom, which enhances the processes of oedema, disorganisation of intracellular structures and the surface apparatus of cardiomyocytes.

In particular, muscle fibres in preparations from this group were more fragmented and disoriented in the plane than in the other experimental group. They thickened, swelled and acquired a tortuous shape. Uneven staining of myocardial fibres, revealed during morphological description, also indicates the development of oedema processes in the sarcoplasm. Striation, and therefore the organisation of intracellular fibres, was finally lost, the fibres were stratified, and the sarcolemma was no longer partially damaged but in places completely absent. All these morphological signs indicate a more pronounced course of oedema, destruction and necrosis processes in cardiomyocytes of animals from this group, which numerically resulted in a significant increase in their size and width. Thus, we can speak of a morphometrically confirmed effect of the venom of the Nikolsky Viper, which in its negative effect surpassed the other studied venom, which resulted in a statistically significant increase in the width of myocardial fibres relative to not only the control but also the second experimental group with the introduction of venom in our study.

To quantitatively assess the condition of the heart wall of rats exposed to the poison, we chose to measure the area occupied by endomysium in cross-sections because it is this connective tissue that directly surrounds the heart muscle fibres and, together with them, reacts to adverse external influences. Moreover, it acts as a barrier on the path of toxic substances directly to cardiomyocytes because it contains the vessels of the microcirculatory bed that carry all substances to and from the heart cells. For an adequate and accurate quantitative assessment of the fate of the endomysium, digital images of sections stained with Picrosirius red were used because this dye is considered the standard for detecting collagen and its quantitative assessment in histological sections of normal and abnormal tissues.

The quantitative assessment of the endomysium area in sections showed a statistically significant increase in both experimental groups compared to the control group (Fig. 2, 3), which confirms the results of morphometric studies of myocardial tissues. In particular, in the experimental groups, an activation of the synthetic activity of fibroblasts was noted, as evidenced by their high nuclear-cytoplasmic index. Such activity led to increased collagen production in the surrounding matrix, forming a network of fibres between cardiomyocytes - we measured its area within the endomysium.

In the control group, the mean endomysial area was 2513.25 μm^2 (first quartile 1886.422 μm^2; third quartile 3018.703 μm^2), while for the group exposed to Vipera berus berus venom, it was 5119.338 μm^2 (first quartile 4013.16 μm^2; third quartile 6234.56 μm^2). This figure is statistically significantly higher than the control group, which is explained by several aspects.

Firstly, as already mentioned, morphological evidence of increased synthetic activity of fibroblasts indicates collagen production within the endomysium. Secondly, during the morphological study of the myocardium of this experimental group, the thickening of the vessel wall, growth of the adventitia of both veins and arteries, which are formed by loose connective tissue, which is woven into the surrounding connective tissue with its collagen fibres, was noted. Accordingly, this also generally leads to an increase in the area of the endomysium within which they lie. Thirdly, the toxic effect of the poison causes the development of oedema processes not only in cardiomyocytes but also in the elements of the endomysium and the walls of the vessels in its composition, their perfusion, loosening and oedema of the intima. Congestive phenomena in the venous system of the myocardium are also morphometrically reflected in a decrease in the part of the area occupied directly by cardiomyocytes to the location of the connective tissue with the vessels included in it.

The average width of cardiomyocytes of animals exposed to the venom of the Nikolsky Viper is 7112.648 μm^2 (first quartile 6346.12 μm^2; third quartile 8137.129 μm^2) - significantly more significant than the corresponding indicator of the control group, while no significant difference in this indicator was observed between the two experimental groups.

These data correspond to our observations of the morphological state of the myocardium of rats from these groups.

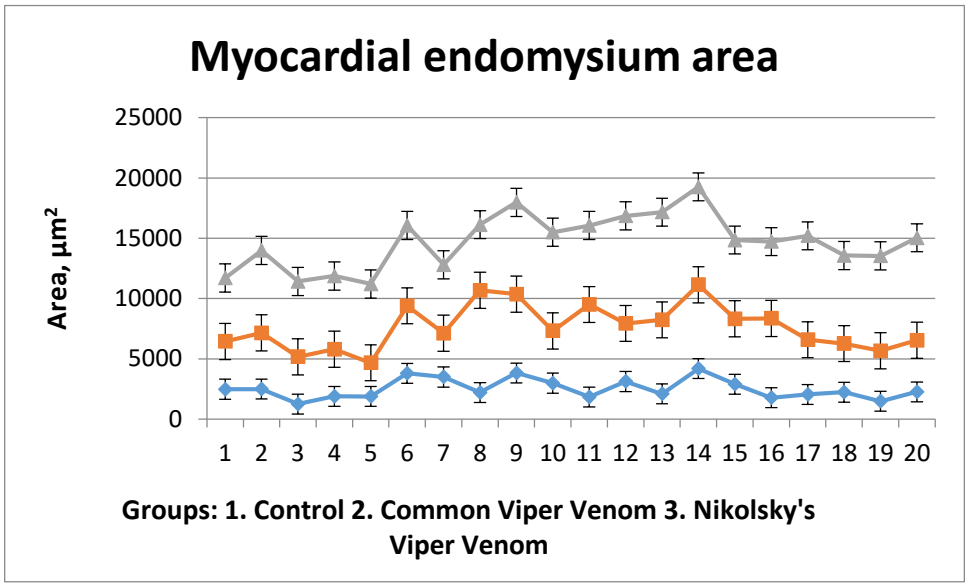

Fig. 2. Individual indicators of the area of endomysium in the myocardium of animals from the control and experimental groups with standard deviation. Row 1 – control group; row 2 – a group introducing the venom of the viper Vipera berus berus; row 3 – a group introducing the venom of the Vipera berus nikolskii.

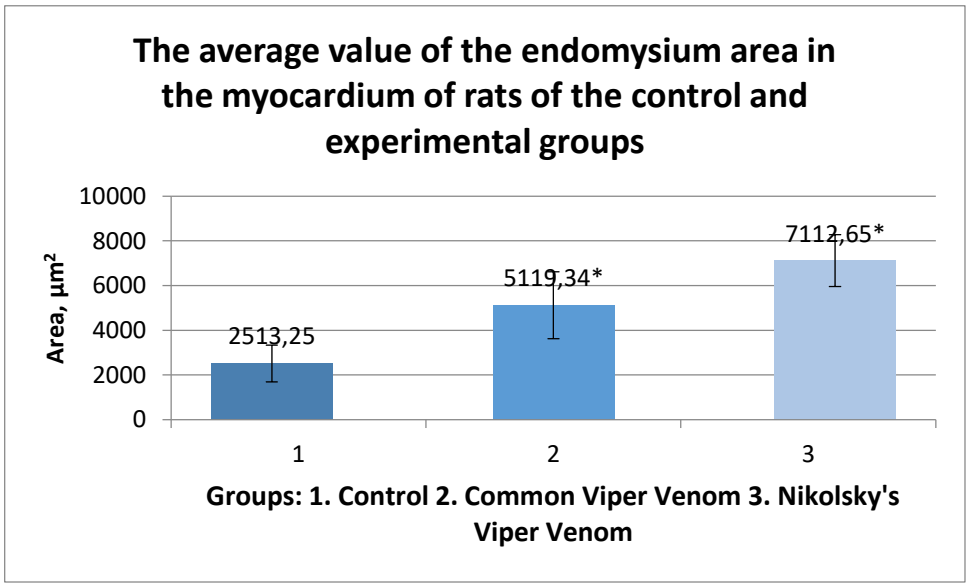

Fig. 3. The average value of the endomysium area of the heart myocardium in the control group, the group with the introduction of Vipera berus berus and Vipera berus nikolskii venom. * - The difference from the control group is significant at p≤0.05.

In particular, this experimental group's foci of necrosis and myocytolysis are surrounded by zones of significant myocardial tissue oedema. The collagen fibres, which we visualised using Picrin red and measured, were added to the total area of connective tissue, as were the adventitia of the vessels, in which collagenisation was noted during the morphological examination. The vessels were dilated and full of blood, increasing their area.

It is important to note that both connective tissue and muscle components of the myocardium are subject to oedema; during the morphological study, we saw a rounded shape and numerous intracellular edemas in them. The nuclei of cardiomyocytes swelled and lost their elongated shape, reflecting a change in the cells' shape. This is also reflected in the statistical data - the absolute values of the endomysium area in both experimental groups are significantly larger than the control; at the same time, the percentage ratio of the area of connective tissue to the total area of the section is not considerably more significant, although

it shows a tendency to increase (Table 1). The fragmentation of cardiomyocytes noted by us during the morphological description of myocardial tissues, which was accompanied by a violation of the integrity of the sarcolemma of these cells, also necessarily led to an increase in their area.

This suggests that, against the background of specific activation of fibroblasts and a corresponding increase in the content of collagen and other connective tissue elements in the extracellular matrix, various factors increasing the area index, in particular oedema, delamination of structures and distortion of their shape, uniformly affect both the connective tissue components of the endomysium and the cardiomyocytes themselves.

Table 1

Indicators of the average endomysium fraction in the myocardium of rats from the control and experimental groups

Group	Control Group	Experimental group with common viper venom	Experimental group with Nikolskii viper venom
Average value and standard deviation, %	10,56±3,47	21,51±6,28	29,88±4,88

Summary

According to the data of morphometric studies, a more pronounced harmful effect of the venom of Vipera berus nikolskii was established, which was manifested in the violation of the structure and shape, oedema of cardiomyocytes, which led to significantly higher indicators of the width of these cells both in comparison with the control group and with the second experimental group. In addition, the action of both venoms, albeit to different degrees, led to the growth of connective tissue elements within the endomysium, which was reflected in an increase in the indicator of the proportion of this tissue in the myocardium. The venoms of both vipers provoked an increase in the proportion of connective tissue in the myocardium; however, against the background of oedema of muscle cells, the relative increase in the area of endomysium to them shows a tendency to increase but is not reliable.

Prospects for further development related to the study of ultrastructural changes in the heart wall of rats exposed to the venom of the vipers Vipera berus berus and Vipera berus nikolskii.

Information on conflict of interest

There are no potential or apparent conflicts of interest related to this manuscript at the time of publication and are not anticipated.

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Бобр А.М. Аналітична і кількісна оцінка стану стінки серця щурів при впливі отрути гадюк *Vipera berus berus* та *Vipera berus nikolskii.*

РЕФЕРАТ. Актуальність. Значна кількість факторів як фізичного, так і хімічного походження можуть чинити негативний вплив на органи серцево-судинної системи. При цьому, реалізація пошкоджуючої дії чинників різного генезу полягає не лише в змінах нормального функціонування серця, але і в запуску складних патогенетичних механізмів, що стають причиною виражених структурних перебудов органу, які подекуди носять незворотній характер. **Мета.** Метою дослідження є аналітична і кількісна оцінка стану стінки серця щурів при впливі отрути гадюк *Vipera berus berus* та *Vipera berus nikolskii*. **Методи.** Експериментальні дослідження проводили на білих нелінійних щурах самцях. Тварин умовно розподіляли на дві групи – контрольну і дослідну по 10 особин в кожній. Дослідним щурам внутрішньоочеревинно вводили напівлетальну дозу (LD_{50}) (1.576 мг· $г^{-1}$) отрути *Vipera berus berus* та *Vipera berus nikolskii* на фізіологічному розчині. Тваринам контрольної групи внутрішньоочеревинно вводили лише фізіологічний розчин. Виводили щурів з експерименту через 24 години після впливу отрути, знеживлюючи шляхом цервікальної дислокації. Для мікроскопічного дослідження забирали зразки серця. Фіксацію матеріалу та приготування парафінових блоків проводили за загальноприйнятими методиками. Фарбування гістологічних препаратів серця здійснювали Picro Sirius Red/Fast Green та гематоксилін-еозином. Для детальної оцінки дії отрути двох видів гадюк на загальний стан серця щурів нами було проведено порівняння абсолютних і відносних змінних, які було виміряно і підраховано відповідно, за допомогою програми Fiji:ImageJ, між контрольною та обома експериментальними групами, що піддавались дії отрут гадюк *Vipera berus berus* та *Vipera berus nikolskii*. Статистична обробка з подальшою побудовою графіків для візуалізації одержаних результатів проводилась у програмі Excel. **Результати та підсумок.** Згідно з даними морфометричних досліджень встановлено більш виражений шкідливий вплив отрути *Vipera berus nikolskii*, що проявлявся у порушенні структури та форми, набряку кардіоміоцитів, які призводили до достовірно вищих показників ширини цих клітин як у порівнянні з групою контролю, так і з другою експериментальною групою. Крім того, дія обох отрут, хоч і різною мірою, призводила до розростання елементів сполучної тканини у межах ендомізію, що відображалось у збільшенні показника частки цієї тканини в міокарді. Отрути обох гадюк провокували підвищення частки сполучної тканини в міокарді, проте на фоні набряклості м'язових клітин, відносне збільшення площі ендомізію до них проявляє тенденцію до збільшення, але не є достовірним.

Ключові слова: гадюки, отрута, серце, саркоплазма, м'язові волокна, щури.