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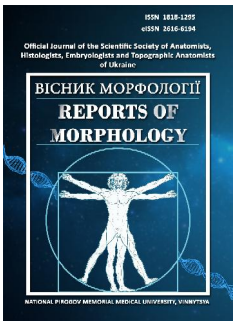

Dynamics of morphological changes in the heart of rats after serial systemic administration of Doxorubicin

Kostiuk O.H.[1], Hodovan N.L.[1], Gormash P.P.[2], Taran I.V.[1], Grebeniuk D.I.[1], Mashevska O.V.[1]

[1]National Pirogov Memorial Medical University, Vinnytsya, Ukraine
[2]Utility non-profit enterprise "Vinnitsa Regional Pathological Bureau of Vinnitsa Regional Council", Vinnytsya, Ukraine

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CORRESPONDING AUTHOR
e-mail: doctor.svo@gmail.com
Grebeniuk D.I.

Along with a good antitumor effect, Doxorubicin has a systemic effect with damage to vital organs, in particular the heart. The lack of a unified approach to dosing and the frequency of administration of Doxorubicin in the experiment prompts the search for an optimal model of Doxorubicin cardiomyopathy. The aim of the study was to develop a method of serial administration of Doxorubicin in medium therapeutic doses in an experiment and to evaluate the cardiotoxic effect of the drug. 42 female Wistar rats were included in the study. The control group consisted of 7 intact rats. The experimental group consisted of 35 rats who received systemic chemotherapy with Doxorubicin at a dose of 5 mg/kg once a week for 5 weeks. On days 7th, 14th, 21st, 28th, 35th, the hearts of experimental animals were taken for morphological examination. Histomorphometrically determined: the diameter of cardiomyocytes (in the middle part) and the transverse diameter of their nucleus, the width of the interstitial space (endo- and perimysia). The data of histomorphological and histomorphometric examination of the myocardium testified that all animals of the experimental group had a circulatory disorder in the heart muscle at the level of hemomicrocirculation. Such changes led to cardiomyocyte hypotrophy, interstitial edema and fibrosis. During systemic chemotherapy, the animals showed marked changes in the myocardium, such as expansion of the endomysial zone, due to capillary congestion and edema, in comparison with animals of the intact group. At the end of the experiment, the animals of the experimental group retained the expansion of the endomysial zone, mainly due to interstitial fibrosis. Such changes indicate myocardial hypoxemia with damage and death of cardiomyocytes, activation of interstitial and replacement collagen formation. The obtained morphological data indicate the development of dilated cardiomyopathy in experimental animals. Serial intraperitoneal administration of Doxorubicin at a dose of 5 mg/kg once a week for 5 weeks causes morphological changes in the myocardium of experimental animals, similar to changes in the heart of people undergoing chemotherapy with this drug.

Keywords: *Doxorubicin, cardiomyopathy, morphology, experiment, rats.*

Introduction

Despite constant scientific and technological progress, the incidence and mortality from cancer are increasing rapidly worldwide [5, 18].

Cancer treatments include surgery, radiation therapy, and systemic treatment, which includes chemotherapy, targeted therapy, hormone therapy, and immunotherapy [5]. Among all methods, pharmacological drugs are the most common means of influencing tumor growth and metastasis and are used in almost all malignant cancers, even in the early stages [6, 8, 9, 10, 11, 22, 23].

Affecting tumor cells, chemotherapeutics creates a systemic toxic effect, which is one of the most significant disadvantages of the use of chemotherapeutics, and even with local administration of drugs [16, 27]. A large number of anticancer drugs affect vital organs, including the heart. The list of cardiotoxic therapeutic agents against cancer includes anthracyclines, trastuzumab, alkylating agents, antimetabolites, tyrosine kinase inhibitors, angiogenesis inhibitors, checkpoint inhibitors and proteasome inhibitors [1, 4, 12].

One of the long-term and widely used drugs with pronounced cardiotoxic effects is a drug of the anthracycline series - Doxorubicin [2, 14, 21]. Good tumor regression with the use of Doxorubicin in both mono and chemotherapy regimens encourages the search for ways to prevent the development of Doxorubicin-induced cardiomyopathy.

The development and implementation of new approaches to the treatment and prevention of pathological conditions, first of all, requires pre-clinical research.

The literature describes a large number of experimental studies related to Doxorubicin-induced cardiomyopathy, but they all differ significantly in the parameters of drug administration [3, 13, 26].

In our opinion, the dosage of Doxorubicin and the frequency of its introduction in the study of its systemic effects, in particular, cardiotoxic effects, should be as close as possible to similar in clinical practice.

The aim of the study was to develop a method of serial administration of Doxorubicin in moderate therapeutic doses in the experiment and to evaluate the cardiotoxic effect of the drug.

Materials and methods

The experimental study was performed on the basis of a research laboratory of preclinical study of pharmacological substances of National Pirogov Memorial Medical University, Vinnytsya. All experiments were performed in accordance with the "Regulations on the Use of Animals in Biomedical Experiments" with the permission of the Bioethics Committee.

The study involved 42 female Wistar rats under 1 year of age and weighing 120 to 220 grams (187.3±13.6 grams). The control group consisted of 7 intact rats, which were selected to determine the main studied morphological and morphometric parameters in the norm. The experimental group consisted of 35 rats, which underwent systemic chemotherapy with Doxorubicin according to the author's method (Patent of Ukraine for utility model № 138091 from 25.11.2019).

The technique consisted of intraperitoneal administration of Doxorubicin at a dose of 5 mg/kg once a week for 5 weeks. The dose of 5 mg/kg was determined by recalculating the average therapeutic dose of the drug for humans in the treatment of superficial bladder cancer. The recalculation was performed according to the method proposed by Anroop B. Nair and Shery Jacob [19].

One week after each administration of the drug (7, 14, 21, 28, 35 days), 7 rats were randomly selected and removed from the experiment by dislocation of the cervical vertebrae under ketamine anesthesia at the rate of 0.22 ml per 100 grams of weight of the experimental animal.

After dissection, the heart was removed, followed by fixation in 10% neutral formalin solution. After fixation for 3 days, cardiac drugs were prepared according to standard methods. Paraffin sections 5-7 μm thick were stained with hematoxylin and eosin. Microscopy and photographing of histological specimens were performed using a light microscope OLIMPUS BX 41 at magnifications of 40x, 100x, 200x, 400x and 1000x. Microscopy assessed the condition of the myocardium, the presence and nature of pathological and compensatory-adaptive changes in it. Images were obtained and processed, morphometry and statistical processing were performed using the program "Quick PHOTO MICRO 2.3". Histomorphometrically determined: the diameter of cardiomyocytes (in their middle part) and the transverse diameter of their nucleus, the width of the interstitial space (endo- and perimysia).

The obtained data were processed using the statistical software package SPSS 20.0 for Windows.

Results

On microscopic examination, the myocardium of the animals of the control group had a characteristic structure of cardiac muscle tissue, without pathological changes. Functional (typical) elements of the myocardium were represented by integral muscle fibers of cardiomyocytes, which in all fields of view were evenly stained with background stain (hematoxylin and eosin), in their peripheral parts was clearly defined cross-striation, not long and less was traced. Inserted discs and lateral anastomoses were visualized between cardiomyocytes. The diameter of cardiomyocytes averaged 11.30±0.10 μm. In the central parts of each cardiomyocyte there were 1-2 nuclei of round-oval shape, with evenly distributed chromatin.

The transverse diameter of the nucleus averaged 3.50±0.19 μm. The stromal component of the myocardium was represented by loose unformed fibrous tissue with vascular and nerve elements, without inflammatory cellular infiltration. Relatively uniform, moderate blood supply, with insignificant venular-capillary predominance

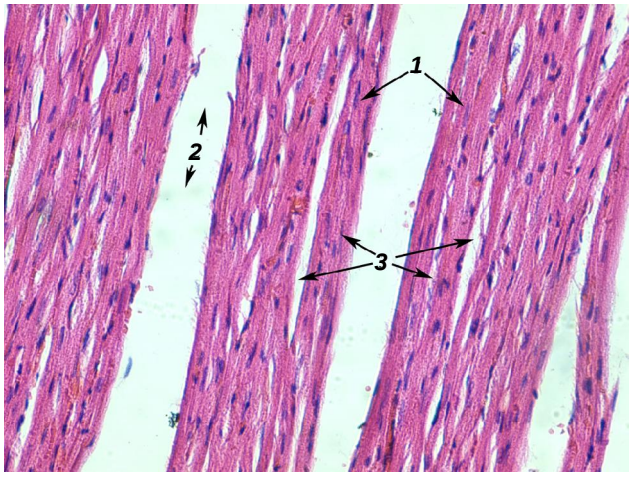

Fig. 1. The rat myocardium of the control group. Hematoxylin-eosin. x200. 1 - cardiomyocytes with a pronounced cross-striation; 2 - perimysium; 3 - endomysium.

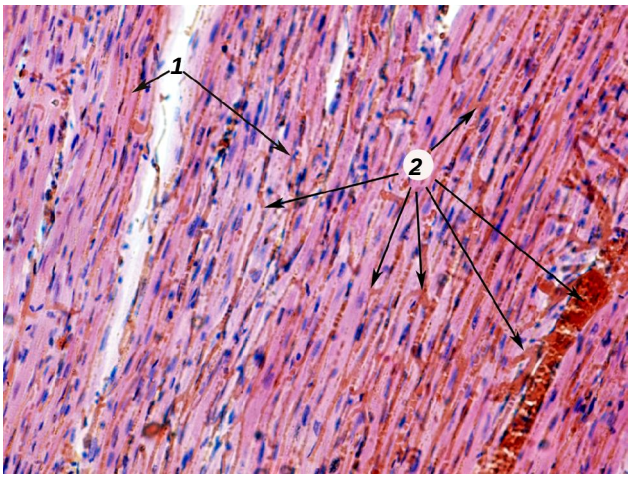

Fig. 2. The rat myocardium of the experimental group on day 7 after systemic chemotherapy. Hematoxylin-eosin. x400. 1 - cardiomyocytes; 2 - pronounced dilation and fullness of blood vessels of hemomicrocirculation.

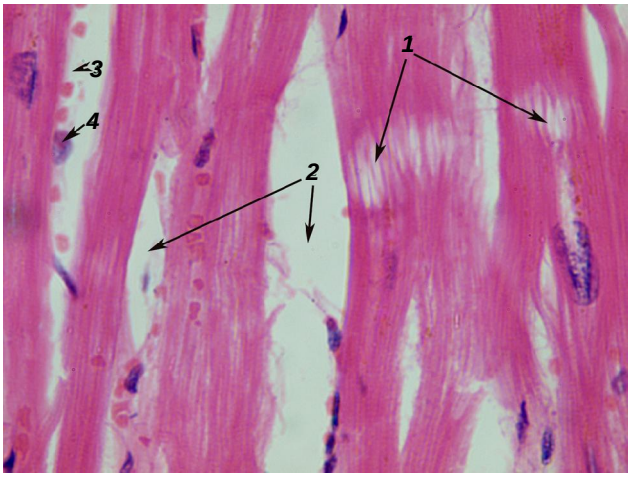

Fig. 3. The rat myocardium of the experimental group on day 7 after systemic chemotherapy. Hematoxylin-eosin. x1000. 1 - vacuolation and defibering of cardiomyocytes; 2 - edema; 3 - blood capillary; 4 - swollen endothelium of the hemocapillary.

was noted in vessels of hemomicrocirculation. The vascular endothelium had a flattened nucleus, almost imperceptible, narrow rim of the cytoplasm (Fig. 1). The width of the endomysium zone averaged 5.40±0.09 μm, perimysium - 28.90±0.22 μm.

On the 7th day of the experiment in the group of animals treated with systemic chemotherapy, there were pronounced changes in the dyscirculatory nature in the form of a significant uniform expansion of the peri- and endomysial zone (33.40±0.10 μm and 16.33±0.33 μm, respectively), indicating interstitial myocardial edema. In vessels of hemomicrocirculation (mainly in venules and capillaries) signs of hyperemia were observed - the expanded gleam of vessels with an unchanged wall was filled with erythrocytes freely located among plasma, and also a stasis - the endothelium of vessels was swollen, the expanded gleam distributed mainly on the periphery of the vessel. In addition, in part of the venules there was a sludge phenomenon (Fig. 2). Small focal diapedetic hemorrhages in perimysia were observed irregularly. If the hyperemia was evenly distributed, the phenomena of stasis, sludge phenomenon and diapedetic hemorrhage were observed more often in the subendocardial parts of the myocardium. There was also swelling of the ventricular endothelium, local subendothelial edema. The average diameter of cardiomyocytes was 8.70±0.21 μm. From a considerable part of cardiomyocytes there was their swelling with the expressed eosinophilic homogenization of a sarcoplasm, basophilic pyknotic nuclei. In this case, more than 50% of the nuclei of preserved cardiomyocytes have condensation of chromatin in the form of a distinct layer with uneven outlines near the nucleus wall, as well as large lumps of chromatin in the center of the nucleus. The transverse diameter of the nuclei averaged 2.20±0.13 μm. No muscle fiber fragmentation was observed. Areas of myofibrillar degeneration and areas with fibrosis and wavy tortuosity of both single and individual groups of muscle fibers were identified. There was also uneven staining with background dyes, deep decay of myofibrils of cardiomyocytes. Some groups of cardiomyocytes had significantly enlightened sarcoplasm (a sign of myocytolysis). There were also single cardiomyocytes with a sharp weakening of tinctorial properties in the central part of the muscle fiber and the preservation of the color of the sarcoplasm in its peripheral areas. The nuclei in such cells had an irregular oval shape. Small foci of a myocardium with express vacuolation of cardiomyocytes, their disintegration without cellular reaction were found (Fig. 3). Most often, these changes were observed in muscle fibers located directly under or near the endocardium.

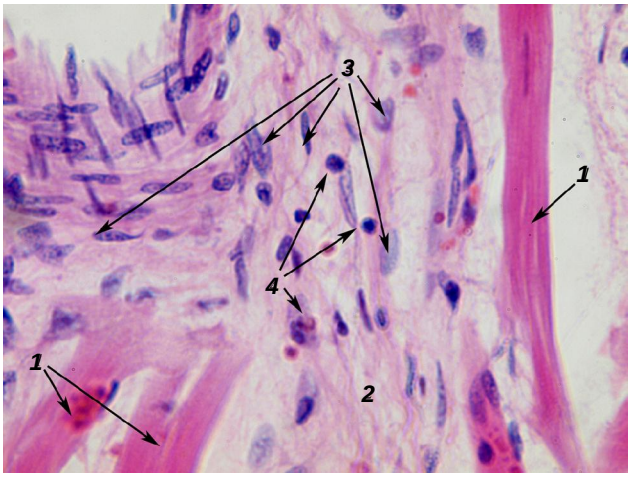

Fig. 4. The rat myocardium of the experimental group on the 14th day after systemic chemotherapy. Hematoxylin-eosin. x1000. 1 - cardiomyocytes; 2 - loose unformed connective tissue interstitium; 3 - active fibroblasts; 4 - lympho-histiocytic elements.

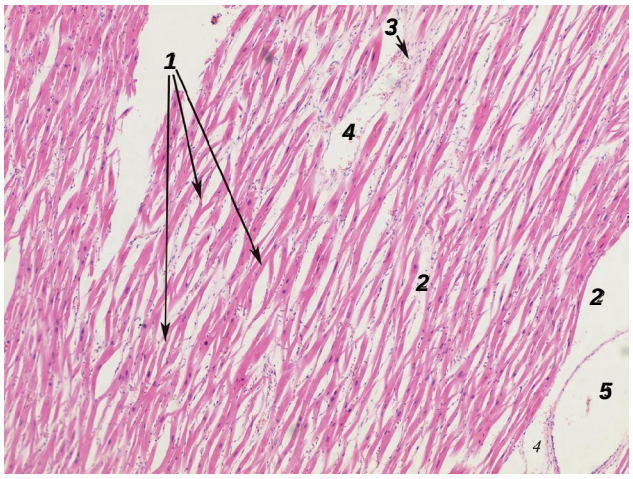

Fig. 5. The rat myocardium of the experimental group for 21 days after systemic chemotherapy. Hematoxylin-eosin. x100. 1 - cardiomyocytes with pronounced anastomoses; 2 - edema of the interstitium; 3 - small-focal fibrosis of the interstitium; 4 - dilated vessels of hemomicrocirculation; 5 - dilated lymphatic vessel.

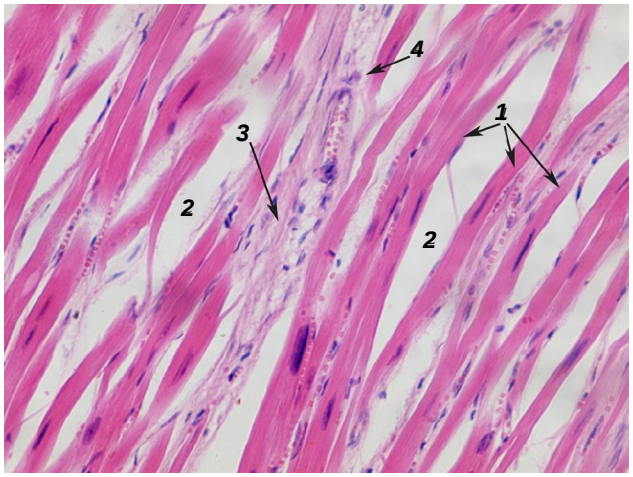

Fig. 6. The rat myocardium of the experimental group for 28 days after the application of systemic chemotherapy. Hematoxylin-eosin. x400. 1 - cardiomyocytes with homogenized sarcoplasm and pyknosis of the nucleus; 2 - swollen endomysium; 3 - perivascular interstitial fibrosis; 4 - plasma cell.

On day 14 of the experiment, in the group of animals treated with systemic chemotherapy, dyscirculatory changes in the form of interstitial edema persisted in the myocardium, although less pronounced (relatively uniform expansion of the peri- and endomysial zone to an average of 39.30±0.25 μm and 10.23±0.22 μm, respectively), as well as signs of uneven capillary-venular plethora, erythrostasis and sludge phenomenon. These pathomorphological changes were most clearly observed in the subendocardial parts of the myocardium. In the stroma, in addition to signs of edema, mainly perivascularly, small-focal clusters of active fibroblasts and thin fibrous fibers were observed, among which a small number of lympho-histiocytic elements were found in some places (Fig. 4). On the part of the muscle fibers, there was a focal fragmentation, defibering and wavy tortuosity, their uneven perception of background stains. Eosinophilic homogenization of sarcoplasm, or, on the contrary, its significant enlightenment, basophilia and pyknosis of nuclei, was preserved in some cardiomyocytes. These changes in myocytes were most often observed subendocardially. The average diameter of cardiomyocytes was 7.30±0.14 μm, the diameter of the nuclei in the cross section was 2.00±0.14 μm.

On the 21st day of the experiment, in the group of animals treated with systemic chemotherapy, the heart muscle showed uneven moderate blood supply and dilatation of the vessels of hemomicrocirculation, places with stasis and erythrocyte sludge. Significant signs of diffuse interstitial edema endo- and perimysia persisted (width 9.82±0.26 μm and 37.40±0.15 μm, respectively). In the latter, the lymphatic vessels had a significantly dilated lumen, with no sign of lymphostasis. In endomysia and perimysia, indistinct foci of excess loose fibrous tissue were observed, represented mainly by a fibrous component with few fibroblasts (including active ones), single lympho-histiocytic elements. Muscle functional fibers of the myocardium, due to endomysia edema, were mostly distant from each other, due to which the anastomoses between them became distinct (Fig. 5).

Some of the fibers and their nuclei had an increased volume (ie, were hypertrophied) and, there was a fragmentation of the fibers, their wavy tortuosity. Most cardiomyocytes had a fuzzy transverse and enhanced longitudinal striation, uneven staining with background stain. In some cardiomyocytes there was their branching and splitting, the presence of vacuolar dystrophy and lysis of the sarcoplasm, condensation of nuclear chromatin and karyopyknosis. In general, the average diameter of cardiomyocytes was 5.10±0.08 μm, the transverse

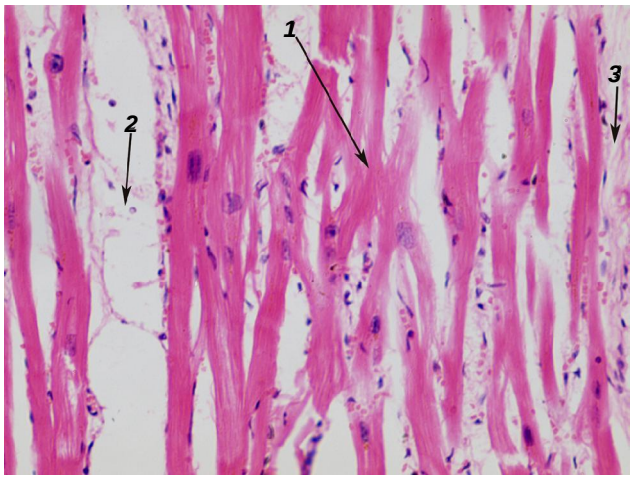

Fig. 7. The rat myocardium of the experimental group for 35 days after systemic chemotherapy. Hematoxylin-eosin. x400. 1 - cardiomyocytes anastomosing; 2 - moderate edema of the interstitium; 3 - focal interstitial fibrosis.

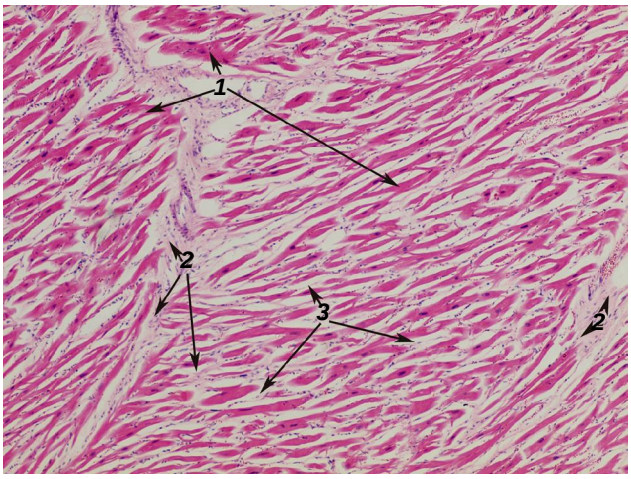

Fig. 8. The rat myocardium of the experimental group for 35 days after systemic chemotherapy. Hematoxylin-eosin. x100. 1 - cardiomyocytes; 2 - fibrous interstitium; 3 - endomysial edema.

diameter of the nuclei - 2.27±0.08 μm.

On the 28th day of the experiment, in the group of animals treated with systemic chemotherapy, the heart muscle showed uniform moderate blood supply to the blood vessels of hemomicrocirculation, erythrostasis and sludge phenomenon were not observed. Although less pronounced, signs of diffuse interstitial edema of the endomysium persisted (on average, the width of the endomysium was 7.50±0.14 μm, and the perimysium was 32.30±0.37 μm). However, the expansion of the endomysium zone was due, in addition to edema, to the presence of excess loose unformed fibrous tissue. In perimysium, foci of fibrosis were observed mainly perivascularly. At the same time, active fibroblasts were found irregularly and in small quantities in the connective tissue, scattered insignificant histio-plasmacytic infiltration was noted (Fig. 6). The functional fibers of the myocardium show an increase in most of them in volume, focal fragmentation, fuzzy transverse and enhanced longitudinal striation, uneven perception of background dyes. In some cardiomyocytes there was defibering, their wavy tortuosity, greater severity of cellular anastomoses. In addition to the increased volume of cardiomyocytes (and, consequently, their nuclei), mostly individual cardiomyocytes and their groups were observed mainly subendocardially, among which there was eosinophilic homogenization of sarcoplasm, basophilia and pyknosis of nuclei. Lipofuscin grains were located perinuclearly in some myocytes. In general, the average diameter of cardiomyocytes was 5.20±0.13 μm, the transverse diameter of the nuclei was 3.30±0.15 μm.

On the 35th day of the experiment in the group of animals treated with systemic chemotherapy, as in the previous period, in the myocardium there was a uniform moderate blood supply to the vessels of hemomicrocirculation, signs of interstitial edema, which was local (mainly in the subendocardial). Dilation of the lumen of lymphatic vessels without signs of lymphostasis was preserved. Also in the interstitium there was a growth of fibrous loose tissue, the fibrous structures of which were relatively thickened, acquired an orderly appearance (located mainly along the functional muscle fibers). Its cellular component was represented by a small number of fibroblasts of varying degrees of activity, single lympho-histiocytic elements. The average width of the endomysium was 7.24±0.08 μm, perimysium - 30.50±0.18 μm. In cardiomyocytes the morphological changes which were noted in the previous term of experiment remained. Namely, the presence of functional fibers of the myocardium and their nuclei increased in volume, with signs of vacuolar and granular dystrophy, lipofuscinosis. The average diameter of cardiomyocytes was 5.50±0.15 μm, the diameter of their nuclei was 3.90±0.16 μm. Focal fragmentation and defibrillation of cardiomyocytes, their wavy tortuosity, the severity of cellular anastomoses due to their dissociation were also preserved (Fig. 7).

At the same time, the number of myocytes with basophilia and nuclear pyknosis decreased. In general, the myocardium retained its structural order. Its architecture was disturbed mainly due to fibrosis and edema of the interstitium (Fig. 8).

Discussion

Doxorubicin belongs to the anthracycline series and has been used as an antitumor drug for almost half a century [20].

Although the use of this drug has shown excellent results in the treatment of malignant tumors, but its wider use is hindered by its potential cardiotoxicity, which is clinically manifested by cardiomyopathy and congestive heart failure [15, 20, 25].

The mechanism of cardiotoxicity of Doxorubicin has not been fully studied. Summarizing the results of a large number of diverse studies, it can be argued that oxidative stress, inflammation, apoptosis, mitochondrial dysfunction and calcium overload of cardiomyocytes are the main components of the pathogenesis of toxic heart disease [7, 17, 24, 28].

The literature describes a large number of experimental studies in which Doxorubicin is administered to develop Doxorubicin-induced cardiomyopathy [3, 13, 26]. However, they all differ significantly in the parameters of drug administration, such as dosage and frequency of its administration.

In our opinion, a large number of differences in the results of Doxorubicin cardiomyopathy studies are due to the variety of dosing methods and the frequency of administration of Doxorubicin.

That is why, in our opinion, an important task is not only the standardization of the method of modeling Doxorubicin-induced cardiomyopathy, but also the maximum approximation of the parameters of the method to those used in clinical practice.

After analyzing modern techniques and not finding one that would fully meet the requirements, we decided to start from proven effective treatment strategies and try to create our own experimental method for modeling Doxorubicin-induced cardiomyopathy.

Our proposed method was intraperitoneal administration of Doxorubicin at a dose of 5 mg/kg once a week for 5 weeks.

The dose of 5 mg/kg was determined by recalculating the average therapeutic dose of the drug for humans in the treatment of superficial bladder cancer. The recalculation was performed according to the method proposed by Anroop B. Nair and Shery Jacob [19].

In general, analyzing the data of histomorphological and histomorphometric examination of the myocardium, we can conclude that in all animals of the experimental group there was, first of all, circulatory disorders in the heart muscle at the level of hemomicrocirculation, which in turn led injury (mainly to dystrophy), predominant cardiomyocyte malnutrition, interstitial edema and fibrosis. Systemic chemotherapy in animals showed marked myocardial changes, such as a threefold enlargement of the endomysal area due to capillary plethora and edema compared with intact animals. At the end of the experiment, the animals of the experimental group maintained an expansion of the endomysial zone to 7.24±0.08 μm, mainly due to interstitial fibrosis. In itself, the expansion of the interstitial zone due to fibrosis indicates, first of all, that in the myocardium there was a significant hypoxemia with damage (including death) of cardiomyocytes, activation of interstitial and replacement collagen formation. The presence of the above changes, such as hypertrophy of the cardiomyocytes on the background of their general malnutrition, interstitial fibrosis, give us reason to argue about the development in experimental animals dilated cardiomyopathy.

In the future, experimental studies are planned on the possibility of reducing the cardiotoxic effects of Doxorubicin.

Conclusions

1. Serial administration of Doxorubicin in medium therapeutic doses according to the proposed method causes changes in the myocardium of experimental animals similar to changes in the heart of people undergoing chemotherapy with this drug.

2. The presence of changes, such as hypertrophy of part of cardiomyocytes against the background of their general malnutrition, interstitial fibrosis, allow to interpret the pathological process in the heart of experimental animals as dilated cardiomyopathy.

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ДИНАМІКА МОРФОЛОГІЧНИХ ЗМІН У СЕРЦІ ЩУРІВ ПРИ СЕРІЙНОМУ СИСТЕМНОМУ ВВЕДЕННІ ДОКСОРУБІЦИНУ

Костюк О.Г., Годован Н.Л., Гормаш П.П., Таран І.В., Гребенюк Д.І., Машевська О.В.

Поряд із хорошим протипухлинним ефектом Доксорубіцин спричиняє системний вплив із ураженням життєво важливих органів, зокрема серця. Відсутність єдиного підходу до дозування та кратності введення Доксорубіцину в експерименті спонукає до пошуку оптимальної моделі доксорубіцинової кардіоміопатії. Мета дослідження - розробити спосіб серійного введення Доксорубіцину у середньотерапевтичних дозах в експерименті та оцінити кардіотоксичний ефект препарату. До дослідження було включено 42 самок щурів лінії Wistar. Контрольну групу склали 7 інтактних щурів. Дослідну групу склали 35 щурів, яким проводили системну хіміотерапію Доксорубіцином у дозі 5 мг/кг 1 раз на тиждень протягом 5 тижнів. На 7, 14, 21, 28, 35 добу вилучали серця піддослідних тварин для морфологічного дослідження. Гістоморфометрично визначали: діаметр кардіоміоцитів (в серединній їх частині) і поперечний діаметр їх ядра, ширину інтерстиціального простору (ендо- та перимізія). Дані гістоморфологічного та гістоморфометричного дослідження міокарда свідчили про те, що у всіх тварин дослідної групи мало місце порушення кровообігу в серцевому м'язі на рівні гемомікроциркуляції. Такі зміни призводили до гіпотрофії кардіоміоцитів, інтерстиціального набряку та фіброзу. При проведенні системної хіміотерапії у тварин відмічалися виражені зміни міокарда такі, як розширення зони ендомізію, за рахунок капілярного повнокрів'я та набряку, у порівнянні з тваринами інтактної групи. Наприкінці експерименту у тварин дослідної групи зберігалось розширення зони ендомізію в основному за рахунок інтерстиціального фіброзу. Подібні зміни вказують на гіпоксемію міокарда з ушкодженням та загибеллю кардіоміоцитів, активацією інтерстиціального та замісного колагеноутворення. Отримані морфологічні дані свідчать про розвиток в експериментальних тварин дилятаційної кардіоміопатії. Таким чином, серійне інтраперитонеальне введення

Доксорубіцину у дозі 5 мг/кг 1 раз на тиждень протягом 5 тижнів викликає морфологічні зміни в міокарді експериментальних тварин аналогічні до змін у серці людей, що проходять хіміотерапію даним препаратом.
Ключові слова: *Доксорубіцин, кардіоміопатія, морфологія, експеримент, щури.*