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Histomorphometric parameters of rat myocardium in doxorubicin-induced cardiomyopathy

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Abstarct. Morphological changes in the structural components of the myocardium were identified in an experimental model of doxorubicin-induced cardiomyopathy. The most informative markers of disease progression were: α-actinin-2 (ACTN2; λ = 0.0051, p = 0.005), cardiac troponin T (TNNT2; λ = 0.0085, p = 0.008), succinate dehydrogenase (SDH; λ = 0.0097, p = 0.010), lactate dehydrogenase (LDH; λ = 0.0135, p = 0.014), and the parenchymal-stromal ratio (PSR; λ = 0.0137, p = 0.014). The obtained data may serve as additional criteria for the detection of the early stage of toxic myocardial damage, as well as for the evaluation of the efficacy of novel cardioprotective agents.

Keywords: doxorubicin-induced cardiomyopathy, ultrastructure, α-actinin-2, cardiac troponin T, succinate dehydrogenase, lactate dehydrogenase, parenchymal-stromal ratio

Introduction

Anthracycline antibiotics are among the most widely used chemotherapeutic agents in oncology [1]. However, the cardiotoxicity of this drug class, which is included in polychemotherapy regimens, leads to the development of cardiovascular diseases both in the early and late rehabilitation periods [2]. The most significant manifestation of such toxicity is considered to be anthracycline-induced cardiomyopathy (CMP), resulting in myocardial dysfunction and remodeling, with possible manifestation years after successful completion of antitumor therapy [3]. The incidence of cardiac injury during treatment with anthracycline antibiotics ranges from 5% to 48%. Mortality from cardiac causes reaches 7%, and in cases of congestive heart failure, it ranges from 27% to 60% [2,4]. These numbers show why cardio-oncology still faces a difficult balance. Doxorubicin, epirubicin, and daunorubicin work well against cancer, but they can also damage the heart, and this risk is hard to avoid. Doxorubicin is used often to treat breast cancer, leukemia, lymphoma, and otherl types of tumors. New drugs, including targeted therapies and immunotherapies, are now available, but they have not really replaced doxorubicin in most clinical treatment plans. Therefore, more cancer survivors are now living with a long-term risk of heart problems, problems that sometimes do not appear until years after treatment ends. Moreover, for a long time, doctors

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managed this risk mainly by limiting the total dose a patient could receive over their lifetime. The reasoning was straightforward: lower doses should cause less harm to the heart. This is why current guidelines set strict limits on cumulative dosing. But long-term studies shows a different results. Even patients who received low or moderate doses can show early signs of heart muscle injury. This injury often stays hidden for years, sometimes decades, before turning into heart failure. Because of this, doctors still do not fully understand when or how this damage builds up over time. More research at the cell level is needed to know when treatment should start.

The pathogenetic mechanisms underlying anthracycline-induced CMP involve the activation of lipid peroxidation, impairment of adrenergic innervation and contractile protein synthesis, development of an immunoinflammatory response, and stimulation of cell death processes in the myocardium [5–8]. Despite the diversity of identified disturbances, characteristic changes in myocardial structure are regarded as the morphological substrate of cardiac dysfunction. These include vacuolization of cardiomyocyte (CMC) cytoplasm, swelling of the sarcoplasmic reticulum and mitochondria, loss of myofibrils, atrophy and lysis of muscle fibers, as well as the development of interstitial fibrosis [9,10]. The aforementioned histopathological transformations lead to an irreversible decrease in left ventricular ejection fraction by 10% from baseline in 26% of patients and to the development of symptomatic heart failure in 7% of patients receiving a cumulative dose of 550 mg/m^2 of doxorubicin (DOX) [11]. A large part of this injury can be traced back to the mitochondria. Doxorubicin has a strong affinity for cardiolipin, a phospholipid found mainly in the inner mitochondrial membrane, and as a result, the drug tends to accumulate primarily within mitochondria rather than elsewhere in the cell. This accumulation disrupts the electron transport chain and drives excessive production of reactive oxygen species (ROS), overwhelming the hearts endogenous antioxidant capacity. A second, largely independent pathway involves DNA damage. Doxorubicin interacts with topoisomerase-II beta (Top2b), an enzyme cardiomyocytes depend on to maintain proper DNA structure, and this interaction leads to double-strand DNA breaks. The resulting damage cause a broad shift in gene expression, with genes involved in mitochondrial biogenesis and sarcomere assembly downregulated, and pro-apoptotic pathways upregulated in turn. Whether the initiating event is oxidative stress or DNA damage, the endpoint is the same cardiomyocyte death. Cardiomyocytes are terminally differentiated and retain minimal regenerative capacity, this loss is, for the most part, irreversible. As cells are progressively lost to apoptosis, necrosis, and autophagy, the myocardium enters a second phase of injury, one marked by activation of cardiac fibroblasts and excessive deposition of collagen and other extracellular matrix proteins. Over time, this remodeling replaces what was once compliant, functional myocardial tissue with stiff, fibrotic scar.

Currently, echocardiographic methods are widely used for the diagnosis of anthracycline-induced CMP, allowing assessment of the functional state of the heart [12]. However, these methods are not always capable of detecting the initial, preclinical stages of myocardial injury, when structural changes have already begun but have not yet resulted in a significant reduction in left ventricular ejection fraction [13]. In this regard, morphological and morphometric analysis methods acquire key importance, enabling precise quantitative assessment of myocardial structural rearrangements at the tissue, cellular, and subcellular levels [14–16]. Circulating biomarkers such as cardiac troponins and brain natriuretic peptide (BNP) are already used clinically to monitor acute cardiomyocyte stress, but their elevations tend to be short-lived and often fail to capture the slow, ongoing structural decline that defines the latent phase of the disease. By the time functional deficits become visible on standard imaging, such as two-dimensional echocardiography, the underlying ultrastructural damage is usually already extensive, and largely irreversible. Animal models therefore remain essential for this kind of work, since they allow longitudinal, invasive

studies that can track the precise histomorphometric course of the disease over time. Because these in vivo models are tightly controlled, researchers can isolate individual variables and assess the myocardium at multiple time points with real rigor. Detailed morphometric profiling, including measures such as the nuclear-cytoplasmic ratio, parenchymal-stromal ratio, and capillary density, offers a much closer look at what is happening within the cellular microenvironment. This kind of quantitative mapping is what ultimately connects molecular-level signaling changes to the gross anatomical dysfunction seen later on.

Despite the availability of data on morphological alterations in anthracycline-induced CMP, many aspects of the relationship between individual histomorphometric parameters and their degree of severity remain insufficiently elucidated. Their diagnostic value deserves particular attention [17–19]. In particular, the relationship between sarcomere structural integrity, reflected by key contractile proteins such as alpha-actinin-2 (ACTN2) and cardiac troponin T (TNNT2), and the metabolic shifts driven by enzymes like succinate dehydrogenase (SDH) and lactate dehydrogenase (LDH), has not yet been fully quantified over time.

Tracking these specific molecular targets using advanced immunohistochemical and electron microscopy techniques makes it possible to identify the point at which compensatory, hypertrophic responses stop being adaptive and instead give way to terminal, maladaptive failure. Establishing clear, quantitative links between these variables would not only deepen our understanding of toxic cardiomyopathy, but also help validate new cellular targets for treatment.

The aim of the present study was to identify correlations between histomorphometric parameters of the rat myocardium in a model of DOX-induced CMP and to determine cellular markers of disease progression.

Materials and Methods

Experimental studies were performed on 80 laboratory male Wistar rats weighing 150–180 g in compliance with legal and ethical standards for animal handling in accordance with national and international quality standards for the planning and conduct of animal studies [20]. A model of experimental CMP was induced by fractional intraperitoneal administration of doxorubicin hydrochloride (RB) at a cumulative dose of 15 mg/kg, divided into 6 injections (2.5 mg/kg each) over 14 days [21]. Experimental animals were divided into groups. Group 1 (n=20, control) received pyrogen-free physiological saline (PFPS). Group 2 (n=30, DOX-CMP-30day) received DOX followed by euthanasia on day 30 after the last drug injection. Group 3 (n=30, DOX-CMP-60day) received DOX followed by euthanasia on day 60 after the last drug injection.

The object of the study was the left ventricular myocardium of the experimental animals. Microspecimens were prepared using a Microm HM 525 cryostat (Germany) and processed using standard histochemical methods for detecting the activity of succinate dehydrogenase (SDH, EC 1.3.99.1) and lactate dehydrogenase (LDH, EC 1.1.1.27) [22]. Quantitative assessment of SDH and LDH enzyme activity was performed using ImageJ software (1.49k, USA).

For histological analysis, tissue samples were fixed in a 10% neutral formalin solution for 48 h, washed in running water, and then processed and embedded in paraffin according to standard protocol [23]. After staining histological sections with hematoxylin and eosin and Masson's trichrome, quantitative assessment of myocardial parenchyma and stroma areas, diameters and cross-sectional areas of CMCs and their nuclei, capillary and arteriole diameters, and arteriolar wall thickness was performed at ×400 magnification using ImageJ software (1.49k, USA). Based on the obtained measurements, the following parameters were calculated: parenchymal-stromal ratio (PSR), nuclear-cytoplasmic ratio (NCR), sclerotic index (SI), trophic index (TI), and Kernohan index (KnI) using the following formulas:

$$PSR = Sp/Ss,, \quad (1)$$

where Sp is the area of myocardial parenchyma, Ss is the area of myocardial stroma;

$$NCR = Sn/Sc, \quad (2)$$

where Sn is the area of the CMC nucleus, Sc is the area of the CMC cytoplasm;

$$SI = (Ss/Sp) \times 100\%, \quad (3)$$

where Ss is the area of myocardial stroma, Sp is the area of myocardial parenchyma;

$$TI = Scap/Sp, \quad (4)$$

where Scap is the area of capillaries, Sp is the area of myocardial parenchyma;

$$KnI = Tw/Rl, \quad (5)$$

where Tw is the thickness of the arteriolar wall, Rl is the radius of the arteriolar lumen.

Immunohistochemical (IHC) staining was performed using polyclonal rabbit antibodies to α-actinin-2 ACTN2 (FNab00121, FineTest, China, working dilution 1:200), cardiac troponin T TNNT2 (E-AB-70232, Elabscience, China, working dilution 1:200), and monoclonal mouse antibodies to α-smooth muscle actin α-SMA (Z2066ML, Zeta Corporation, USA, working dilution 1:200). All stages of the IHC study were performed according to the manufacturer's protocol. Detection was performed using the 2-step plus Poly-HRP Anti Rabbit IgG Detection System (E-IR-R217, Elabscience, China). A 1% solution of 3,3-diaminobenzidine tetrachloride served as the chromogen. Microspecimens were digitized using a MoticEasyScan One histological scanner (China) at ×20.0 magnification. Quantitative assessment of IHC results was performed using Aperio ImageScope image analysis software [v12.4.6.5003] by selecting 10 random non-overlapping fields of view at ×200 magnification. Parameters were analyzed using the standard PositivePixelCount v9 algorithm [24]. The following expression parameters were assessed:

Percent positivity – ratio of the number of positive pixels to the total number of positive and negative pixels × 100%;

Nsr – proportion of pixels with high intensity in immunopositive areas;

Intensity coefficient – ratio of the sum of products of the number of positive pixels and the score equivalent corresponding to their intensity (no IHC reaction – 0 points, weak – 1 point, moderate – 2 points, strong – 3 points) to the total number of positive pixels;

Isr – proportion of the total intensity level of highly positive pixels.

An electron microscopic method was also used in the study [25]. Sections were prepared using an LKB-8800 ultramicrotome (Sweden) and examined using a JEM-100 CX electron microscope (Jeol, Japan). Morphometric analysis of electron micrographs was performed using ImageJ data processing software (1.49k, USA). The following parameters were assessed: number of mitochondrial profiles per section, mean area of one mitochondrion per section (μm^2), ratios of the total cross-sectional areas of mitochondria and myofibrils per section to the total CMC area, which determine the volume fraction of mitochondria and myofibrils in the CMC volume (%), number of intermitochondrial contacts (IMCs) per 100 mitochondria, cross-sectional area

of myocardial capillaries (μm^2). The parameter of CMC energy supply was calculated as the ratio of the volume fraction of mitochondria to the volume fraction of myofibrils.

The obtained morphometric data were processed using methods of variation statistics (STATISTICA 12.0 software package, StatSoft, USA). The distribution of quantitative traits for conformity to the normal distribution model was tested using the Shapiro-Wilk W-test. Given the absence of normal distribution in most of the studied samples, the relationship between parameters was assessed using the nonparametric two-tailed Spearman correlation coefficient (rs). Discriminant analysis was used to determine the informational (diagnostic) value of the studied morphometric parameters. The indicator of informativeness of features is the partial Lambda (λ) [19]. Differences were considered significant at a significance level of $p \leq 0.05$.

Results

At the tissue level, during the development of DOX-induced CMP by day 30 of observation, correlational relationships were identified between parameters of the myocardial parenchyma and stroma. Positive correlations were found between the PSR parameter and the volume fraction of myofibrils and the percent positivity of ACTN2 expression in CMCs, as well as negative correlations between the SI and the same parameters. Inverse correlations were recorded between the intensity of α-SMA expression in the myocardial stroma and the intensity of ACTN2 expression, Nsr ACTN2, and Isr ACTN2 in CMCs. On the part of the microcirculatory bed, inverse correlations were noted between the CMC area and the capillary cross-sectional area, as well as between the percent positivity of ACTN2 expression and the KnI. A positive correlation was found between the percent positivity of ACTN2 expression and the arteriolar lumen diameter.

At the cellular level, correlational relationships reflecting compensatory and metabolic remodeling of CMCs were established. The CMC area directly correlated with the CMC nuclear area and SDH, while the nuclear area, in turn, was associated with the NCR. The CMC diameter showed a strong positive correlation with the number of IMCs, as well as direct relationships with SDH and LDH activity. At the same time, a negative correlation was found between the NCR and LDH activity. A positive correlation was recorded between the percent positivity of ACTN2 expression and the IMC parameter.

At the subcellular level, correlations characterizing the state of the contractile and energy apparatuses of CMCs were identified. The volume fraction of myofibrils inversely correlated with the ratio of the volume fractions of myofibrils and mitochondria and the number of mitochondrial profiles per section, but positively correlated with the intensity of TNNT2 expression. The volume fraction of mitochondria, in contrast, was positively correlated with the myofibril/mitochondria ratio and negatively correlated with the number of IMCs. The number of mitochondrial profiles directly correlated with LDH activity. Simultaneously, positive correlations were recorded between SDH activity and ACTN2 expression (Nsr/Isr) and TNNT2 expression (Nsr/Isr) (Table 1).

Table 1

Correlational relationships between morphometric parameters of rat myocardium with DOX-induced CMP at day 30 of observation

First-order parameter	Second-order parameter	Correlation coefficient	Significance level
Tissue level			

PSR	Volume fraction of myofibrils	0,38	p = 0,039*
	Volume fraction of myofibrils	0,34	p = 0,046*
SI	Volume fraction of myofibrils	-0,38	p = 0,039*
	Volume fraction of myofibrils	-0,34	p = 0,046*
Intensity of α-SMA expression	Intensity of ACTN2 expression	-0,48	p = 0,022*
	Nsr ACTN2	-0,47	p = 0,029*
	Isr ACTN2	-0,47	p = 0,029*
CMC area	Capillary cross-sectional area	-0,50	p = 0,005*
Percent positivity of ACTN2 expression	Arteriolar lumen diameter	0,43	p = 0,018*
	KnI	-0,38	p = 0,041*
Cellular level			
CMC area	CMC nuclear area	0,39	p = 0,001*
	SDH	0,34	p = 0,007*
CMC diameter	IMC	0,79	p = 0,007*
	SDH	0,26	p = 0,041*
	LDH	0,25	p = 0,049*
CMC nuclear area	NCR	0,62	p = 0,001*
NCR	LDH	-0,38	p = 0,003*
Percent positivity of ACTN2 expression	IMC	0,71	p = 0,021*
Subcellular level			
Volume fraction of myofibrils	Ratio of volume fractions of myofibrils/ mitochondria	-0,58	p = 0,001*
	Number of mitochondrial profiles per section	-0,36	p = 0,049*
	Intensity of TNNT2 expression	0,37	p = 0,047*
Volume fraction of mitochondria	Ratio of volume fractions of myofibrils/ mitochondria	0,72	p = 0,001*
	IMC	-0,73	p = 0,017*
Number of mitochondrial profiles per section	LDH	0,49	p = 0,006*
SDH	Nsr ACTN2	0,35	p = 0,037*
	Isr ACTN2	0,36	p = 0,032*
	Nsr TNNT2	0,38	p = 0,020*
	Isr TNNT2	0,38	p = 0,020*

Note: Significance of differences: * – second-order parameters.

At day 60 of DOX-induced CMP development, at the tissue level, correlational relationships were found indicating the progression of fibrotic remodeling and deepening of metabolic rearrangement of the myocardium. A negative correlation was identified between the area of the parenchyma and the area of the myocardial stroma. Positive correlations were established between the PSR parameter and the TI and LDH activity, as well as a negative correlation between PSR and SDH activity. For the SI, inverse relationships were recorded: negative correlations with TI and LDH, but a positive correlation with SDH. Inverse relationships were identified between the percent positivity of α-SMA expression in the myocardial stroma and the expression of the

contractile proteins ACTN2 and TNNT2 in CMCs. At the same time, the intensity of α-SMA expression positively correlated with LDH activity. A direct correlation was found between the capillary cross-sectional area and SDH activity.

At the cellular level, correlational relationships were established reflecting disruption of nuclear-cytoplasmic homeostasis and maladaptive remodeling of CMCs. The CMC area positively correlated with the nuclear area, but negatively correlated with the NCR and LDH activity. The CMC diameter showed a strong positive correlation with the number of IMCs and a negative correlation with the NCR. The CMC nuclear area directly correlated with the NCR and the volume fraction of mitochondria, while the nuclear diameter was negatively correlated with LDH activity. A positive correlation was noted between the NCR and the percent positivity of TNNT2 expression, as well as a negative correlation between the percent positivity of ACTN2 expression and the number of IMCs.

At the subcellular level, correlations were identified characterizing the disintegration of the contractile and energy apparatuses of CMCs. The volume fraction of myofibrils inversely correlated with the ratio of the volume fractions of myofibrils/mitochondria, but positively correlated with the number of IMCs. The volume fraction of mitochondria, in contrast, was directly correlated with the myofibril/mitochondria ratio, the mean area of one mitochondrion, and the number of mitochondrial profiles. A positive correlation was recorded between SDH and LDH activity, as well as a negative correlation between the percent positivity of ACTN2 expression and SDH activity, with simultaneous positive correlations with TNNT2 expression parameters (Table 2).

Using discriminant analysis, the informational (diagnostic) value of the studied morphometric parameters was determined. The most informative were: ACTN2 expression ($\lambda = 0.0051$, $p = 0.005$), followed in descending order by TNNT2 expression ($\lambda = 0.0085$, $p = 0.008$), SDH activity ($\lambda = 0.0097$, $p = 0.010$), LDH activity ($\lambda = 0.0135$, $p = 0.014$), and PSR ($\lambda = 0.0137$, $p = 0.014$).

Table 2

Correlational relationships between morphometric parameters of rat myocardium with DOX-induced CMP at day 60 of observation

First-order parameter	First-order parameter	Correlation coefficient	Significance level
Tissue level			
Area of parenchyma	Area of stroma	-0,99	$p = 0,001$*
PSR	TI	0,30	$p = 0,035$*
	SDH	-0,32	$p = 0,022$*
	LDH	0,39	$p = 0,006$*
SI	TI	-0,30	$p = 0,035$*
	SDH	0,32	$p = 0,022$*
	LDH	-0,39	$p = 0,006$*
Percent positivity of α-SMA expression	Percent positivity of ACTN2 expression	-0,37	$p = 0,032$*
	Intensity of ACTN2 expression	-0,35	$p = 0,047$*
	Intensity of TNNT2 expression	-0,45	$p = 0,009$*

Intensity of α-SMA expression	LDH	0,41	$p = 0,017$*
Capillary cross-sectional area	SDH	0,49	$p = 0,006$*
Cellular level			
CMC area	CMC nuclear area	0,40	$p = 0,001$*
	NCR	-0,27	$p = 0,001$*
	LDH	-0,22	$p = 0,049$*
CMC diameter	NCR	-0,13	$p = 0,004$*
	IMC	0,68	$p = 0,029$*
CMC nuclear area	NCR	0,73	$p = 0,001$*
	Volume fraction of mitochondria	0,40	$p = 0,028$*
CMC nuclear diameter	LDH	-0,22	$p = 0,047$*
NCR	Percent positivity of TNNT2 expression	0,34	$p = 0,038$*
Percent positivity of ACTN2 expression	IMC	-0,87	$p = 0,001$*
Subcellular level			
Volume fraction of myofibrils	Ratio of volume fractions of myofibrils/mitochondria	-0,76	$p = 0,001$*
	IMC	0,72	$p = 0,019$*
Volume fraction of mitochondria	Ratio of volume fractions of myofibrils/mitochondria	0,70	$p = 0,001$*
	Mean area of one mitochondrion per section	0,38	$p = 0,039$*
	Number of mitochondrial profiles per section	0,52	$p = 0,004$*
SDH	LDH	0,44	$p = 0,001$*
Percent positivity of ACTN2 expression	SDH	-0,71	$p = 0,001$*
	Intensity of TNNT2 expression	0,54	$p = 0,001$*
	Nsr TNNT2	0,51	$p = 0,002$*
	Isr TNNT2	0,51	$p = 0,002$*

Note: Significance of differences: * – second-order parameters.

Discussion

Correlation analysis of the parameters of myocardial structural components in the dynamics of DOX-induced CMP development allowed the identification of the main patterns of morphogenesis of toxic CMP. The identified relationships, encompassing myocardial remodeling at the tissue, cellular, and subcellular levels, are consistent with current concepts of the mechanisms of toxic cardiac remodeling, in which mitochondrial dysfunction, metabolic transformation of CMCs, and myocardial fibrosis serve as key links [5–7].

By day 30 of the development of simulated CMP in rat myocardium, fibrotic changes in the stroma, coupled with suppression of CMC contractile function, assume a dominant role at the tissue level. A marker of developing fibrosis is the inverse correlations between α-SMA expression in the stroma and ACTN2 expression parameters in CMCs, reflecting the activation of myofibroblasts as CMCs lose their functional potential. According to the literature, DOX-induced oxidative stress triggers signaling pathways (TGF-β1/R-Smad) that stimulate fibroblast differentiation into myofibroblasts [26]. The negative correlation between CMC area and capillary cross-sectional area indicates the development of relative ischemia due to angiogenesis lagging behind muscle fiber growth [27]. This imbalance is confirmed by the inverse correlation between ACTN2 expression and KnI, indicating microcirculatory deterioration against the background of reduced CMC contractile potential. The positive correlation between percent positivity of ACTN2 expression and arteriolar lumen diameter likely represents a compensatory reaction aimed at maintaining blood supply under conditions of parenchymal damage. Nevertheless, the persisting imbalance in the "parenchyma – microcirculatory bed" system remains a significant factor in the pathogenesis of DOX-induced CMP.

The positive correlational relationships recorded at the cellular level between CMC area and their nuclear area, as well as between CMC nuclear area and NCR, indicate the development of compensatory hypertrophy aimed at maintaining CMC contractile function under conditions of increased functional load caused by the cardiotoxic effect of DOX. The direct correlation between CMC diameter and the number of IMCs reflects an adaptive rearrangement of the energy-producing system: the formation of IMCs ensures coordination of mitochondrial functions and integration of their energy potential, thereby contributing to adequate energy supply of the hypertrophied cell [28]. At the same time, the positive correlation between CMC diameter and LDH activity reveals a metabolic shift in which the progression of hypertrophy against a background of hypoxia is accompanied by activation of anaerobic glycolysis. Such a switch in energy metabolism from fatty acid oxidation to glycolysis is characteristic of heart failure and serves as an adaptive mechanism for maintaining energy production under oxygen deficiency [29].

At the subcellular level, the identified disturbances indicate the key role of mitochondrial dysfunction in mediating the cardiotoxic effect of anthracyclines. The negative correlation between the volume fraction of myofibrils and the number of mitochondrial profiles, as well as the correlation of the latter with LDH activity, indicate structural degradation of energy-producing organelles. DOX is known for its ability to accumulate in mitochondria, interact with cardiolipin, and disrupt respiratory chain function, leading to decreased activity of oxidative enzymes and excessive generation of reactive oxygen species [5,6]. At the same time, the preservation of positive correlations between SDH activity and expression of contractile proteins (ACTN2, TNNT2) reflects an attempt by the cell to maintain the contractile apparatus under conditions of increasing energy deficit. However, the uncoupling of energy production and energy consumption processes inevitably leads to a decline in contractile function and progression of heart failure. Thus, by day 30 of DOX-induced CMP development, the obtained data demonstrate the formation of a pathological cascade: mitochondrial damage initiates an energy deficit, which stimulates hypertrophy and a metabolic shift at the cellular level, while CMC death against a background of impaired microcirculation triggers remodeling of the myocardial stroma at the tissue level.

By day 60 of the experiment, correlation analysis revealed a qualitatively different picture compared to day 30 of observation, reflecting the progression of the pathological process and the transition from the compensation stage to the stage of decompensation and profound myocardial remodeling. At the tissue level, a strong inverse correlation between parenchymal and stromal area draws attention, indicating replacement fibrosis. The increase in connective tissue

volume occurs strictly proportionally to the loss of functioning CMCs, which corresponds to the picture of diffuse cardiosclerosis in the terminal stages of anthracycline-induced CMP [30]. The multidirectionality of the correlational relationships of PSR and SI with metabolic markers reflects the heterogeneity of the tissue response. The positive correlation of PSR with LDH activity, combined with a negative correlation with SDH, indicates a compensatory switch of metabolism in the remaining parenchyma to anaerobic glycolysis under hypoxic conditions. Conversely, the opposite dynamics for SI characterize zones of pronounced fibrosis, where the glycolytic activity of individual CMCs is suppressed due to critical depletion of metabolic reserves and profound microcirculatory disturbance. Fibrous replacement of functional tissue is evidenced by negative correlations of α-SMA expression with CMC contractile proteins (ACTN2, TNNT2), while the positive correlation of α-SMA with LDH indicates the coupling of fibrogenesis with local tissue hypoxia. In contrast to day 30, where compensatory vasodilation was observed (correlation of ACTN2 expression with arteriolar diameter), by day 60 fibrosis becomes the dominant factor disrupting microcirculation. The positive correlation between capillary cross-sectional area and SDH activity likely represents a terminal compensatory reaction aimed at maintaining oxygenation of remaining hypertrophied CMCs; however, against the background of decreased PSR and increased SI, this reaction is insufficient.

At the cellular level, the identified correlations indicate depletion of CMC adaptive reserves and a transition from compensatory hypertrophy to dystrophic changes. The preservation of a positive correlation between CMC area and nuclear area, together with a simultaneous negative correlation of cell area with NCR, indicates an imbalance in nuclear-cytoplasmic relationships: cytoplasmic growth outstrips the functional capacity of the nuclear apparatus, leading to accumulation of excessive cytoplasmic mass not supported by adequate transcriptional control and energy supply [31]. The decrease in NCR with increasing CMC diameter also confirms the depletion of cellular synthetic resources. The paradoxical dynamics of mitochondrial integration deserve particular attention. The strong direct correlation between CMC diameter and the number of IMCs, at first glance, reflects an adaptive rearrangement of the energy apparatus aimed at maintaining the contractile function of the hypertrophied cell [28]. However, the simultaneous pronounced negative correlation between ACTN2 expression and IMCs reveals a fundamentally different pattern: the formation of IMCs at day 60 of the experiment is associated with degradation of the CMC contractile apparatus. This indicates that mitochondrial integration occurs predominantly in CMCs with pronounced myofibrillar damage, likely as an emergency compensatory reaction aimed at overcoming energy deficit; however, this reaction is unable to prevent structural disintegration and progression of functional insufficiency.

At the subcellular level, the identified relationships demonstrate a profound imbalance between the myofibrillar and mitochondrial apparatuses. The negative correlation between the volume fraction of myofibrils and the myofibril/mitochondria ratio indicates that contractile structures are lost more rapidly than energy structures, which is characteristic of the terminal stage of heart failure [29]. The positive correlation of the volume fraction of mitochondria with their number and mean area may be regarded as compensatory mitochondrial hyperplasia; however, against the background of the negative correlation between ACTN2 and SDH, an uncoupling between energy production and energy consumption becomes evident.

The key integrative marker of disorganization at day 60 of the experiment is ACTN2, a structural protein of sarcomeres that ensures stability of the CMC contractile apparatus. Its expression negatively correlates with the number of IMCs, SDH activity, and α-SMA expression in the stroma. A decrease in ACTN2 is associated with impaired blood supply, decline in aerobic metabolism, and activation of fibrogenesis. Positive correlations of ACTN2 with TNNT2 expres-

sion parameters suggest a staged degradation of sarcomeric proteins: ACTN2 is degraded earlier, while troponin T maintains expression for a longer period.

Thus, by day 60 of DOX-induced CMP development, the nature of the pathological process changes: compensatory-adaptive reactions that predominated at the early stage are replaced by maladaptive remodeling. Progressive fibrosis at the tissue level exacerbates capillary dysfunction and tissue hypoxia, which stimulates a metabolic shift toward anaerobic glycolysis. At the cellular level, this is accompanied by CMC dystrophy, manifested by a decrease in NCR and suppression of contractile protein expression, while at the subcellular level, structural disintegration is observed, characterized by dissociation between hyperplasia of the mitochondrial apparatus and degradation of myofibrils. Collectively, the identified changes indicate depletion of myocardial adaptive reserves, determining the irreversibility of toxic damage and the transition to decompensation of cardiac function.

Conclusion

Within the framework of the conducted study, features of myocardial morphogenesis in experimental cardiomyopathy induced by doxorubicin were identified. The most informative prognostic parameters were established, which may be used for the detection of the early stage of toxic myocardial damage, as well as for the development of effective cardioprotective agents.

Author contributions

E.F. – conducting experiments, writing the article; S.M. – editing the manuscript, approval of the final version for publication.

Conflict of Interest

The authors declare no conflicts of interest.

Compliance with ethical standards

All procedures performed in studies involving animals were in accordance with the ethical standards of the institution at which the studies were conducted and with approved international regulations.

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Егеуқұйрық миокардының доксорубицин-индуцирленген кардиомиопатиясы кезінде гистоморфометриялық көрсеткіштері

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Аңдатпа. Доксорубицин тудырған кардиомиопатияның эксперименттік моделінде миокардтың құрылымдық компоненттеріндегі морфологиялық өзгерістер анықталды. Аурудың өршуінің ең ақпараттық маркерлері болды: α-актинин-2 (ACTN2; λ = 0,0051, *p* = 0,005), жүрек тропонині Т (TNNT2; λ = 0,0085, *p* = 0,008), сукцинатдегидрогеназа (**СДГ;** λ = 0,0097, *p* = 0,010), лактатдегидрогеназа (**ЛДГ;** λ = 0,0135, *p* = 0,014) және паренхималық-стромальды қатынас (ПСО; λ = 0,0137, *p* = 0,014). Алынған деректер миокардтың уытты зақымдануының ерте сатыларын анықтауға, сондай-ақ жаңа кардиопротекторлық агенттердің тиімділігін бағалауға қосымша критерий ретінде қызмет етуі мүмкін.

Түйін сөздер: доксорубицин тудырған кардиомиопатия, ультрақұрылым, α-актинин-2, жүрек тропонині Т, α-тегіс бұлшықет актині, паренхималық-стромальды қатынас.

Гистоморфометрические показатели миокарда крыс при доксорубицин-индуцированной кардиомиопатии

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Аннотация. Установлены морфологические изменения структурных компонентов миокарда в экспериментальной модели кардиомиопатии, индуцированной доксорубицином. Наиболее информативными маркерами прогрессирования заболевания оказались: α-актинин-2 (ACTN2; λ = 0,0051, p = 0,005), сердечный тропонин Т (TNNT2; λ = 0,0085, p = 0,008), сукцинатдегидрогеназа (СДГ; λ = 0,0097, p = 0,010), лактатдегидрогеназа (ЛДГ; λ = 0,0135, p = 0,014) и показатель паренхиматозно-стромального отношения (ПСО; λ = 0,0137, p = 0,014). Полученные данные могут быть дополнительными критериями для выявления ранней стадии токсического повреждения миокарда, а также для оценки эффективности новых кардиопротекторных средств.

Ключевые слова: доксорубицин-индуцированная кардиомиопатия, ультраструктура, α-актинин-2, сердечный тропонин Т, сукцинатдегидрогеназа, лактатдегидрогеназа, паренхиматозно-стромальное отношение

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