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Autophagy Activity in Epicardial Cells in Acute Pericarditis

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Summary

Pericarditis is a group of polyetiological diseases often associated with emergence of life–threatening conditions. Poor knowledge of underlying cellular mechanisms and lack of relevant approaches to investigation of pericarditis result in major challenges in diagnosis and treatment.

The aim of this work was to identify changes in the activity of autophagy in epicardial cells in acute pericarditis.

Materials and methods. Acute pericarditis in mice was induced by intrapericardial injection of Freund's adjuvant in the study group (*N*=15). The control group included animals receiving either intrapericardial injection of phosphate-buffered saline (PBS) (*N*=15), or sham surgery without injections (*N*=7). On Days 3 or 5 after surgery the animals were euthanized under isoflurane anesthesia. Immunofluorescence staining of cardiac tissue cryo-sections and immunoblotting were used to assess the intensity of inflammation and autophagy in the epicardium.

Results. Inflammation and other signs of acute pericarditis resulting in thickening of some epicardial areas were found: 68±9% in the control (after PBS injection) and 124±22% after Freund's adjuvant injection (*P*=0.009); other signs included cellular infiltration of epicardium and multiple adhesions. The epicardial layer exhibited signs of mesothelial cells reorganization with 11-fold increase of autophagy markers LC3 II/LC3 I ratio: 0.07±0.02 in the control group (after PBS injection) and 0.84±0.07 — in acute pericarditis (*P*=0.04), and accumulation of collagen fibers.

Conclusion. Development of acute pericarditis is accompanied by activation of epicardial mesothelial cells, intensified autophagy and development of fibrous changes in epicacardial/ subepicardial areas.

Keywords: autophagy; acute pericarditis; epicardium

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Pericarditis is an inflammatory condition of the serous membranes of the heart characterized by thickening, fusion, and fibrotic transformation of the pericardial layers, which can lead to heart chamber compression and their abnormal diastolic filling [1–3]. It is a fairly common clinical finding during the evaluation of hospitalized patients with chest pain, dyspnea, and other signs of heart failure. According to the literature, pericarditis is found in 0.1–0.2% of hospitalized patients with nonischemic chest pain, and acute pericarditis is diagnosed in 5–7% of emergency department admissions [3, 4].

According to biopsy data, fibrotic changes of the visceral pericardial layer (epicardium) are found in most cases, regardless of the etiology. These changes are often accompanied by fibrosis in the underlying myocardial layers and subsequent heart failure [5, 6]. The progression of fibrosis to the underlying myocardium associates with a poor prognosis [7–9]. The therapy for these patients is often chosen based on the nature of the disease, with treatment limited to prescribing non-steroidal anti-inflammatory drugs and colchicine [10]. This is largely due to the fact that many aspects of the pathogenesis of pericarditis remain poorly understood, as do the cellular mechanisms of its development.

According to recent research, one of the mechanisms of cellular response to the inflammatory microenvironment is an alteration in autophagy activity [11, 12]. Autophagy is an evolutionarily conserved mechanism that, at a basic level, helps to maintain cellular homeostasis by utilizing macromolecules and organelles via the lysosomal degradation pathway [13, 14]. Under stress, autophagy

can help cells survive by providing a temporary cellular adaptation to unfavorable conditions, but excessive activation has the opposite effect, resulting in cell death and the development of abnormalities such as fibrosis.

The aim of the study was to identify changes in autophagy activity in epicardial cells during acute pericarditis.

Materials and Methods

Modeling of acute pericarditis. Acute pericarditis was modeled *in vivo* in male C57BL/6 mice (*N*=37, age 8 weeks, weight 28–30 g). Animal experiments were performed in accordance with the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (Strasbourg, March 18, 1986, ETS 123), International Guiding Principles (Code of Ethics) for Biomedical Research Involving Animals, developed and published in 1985 by the Council for International Organizations of Medical Sciences (CIOMS), Rules for Conducting Research Using Experimental Animals, approved by the Appendix to the Order of the Ministry of Health of the USSR No. 755 dated August 12, 1977. Animals were maintained on a standard diet and had free access to water. Surgery was performed under aseptic conditions under general anesthesia (Avertin, intraperitoneal injection). Mice were intubated and placed on a ventilator (MiniVent, Hugo Sachs Elektronik/Harvard Apparatus, Germany). After preparation of the surgical field, a longitudinal skin incision was made along the anterior midline from the angle of the sternum to the base of the xiphoid process. The underlying tissues were separated by blunt dissection. After exposing the outer surface of the intercostal muscles, a horizontal incision was made in the 9th intercostal space from the sternocostal joint to the mid-axillary line to enter the thoracic cavity and provide access to the heart. Study group animals (*N*=15) were injected intrapericardially with 50 µL complete Freund's adjuvant under visual guidance using a Leica M620 surgical microscope. The control animals were injected intrapericardially with 50 µL phosphate-buffered saline (*N*=15) or underwent surgery without intrapericardial injection of any drug (sham-operated animals, *N*=7). The wound was then sutured layer by layer. On day 3 or 5 after surgery, animals were euthanized by cervical dislocation after inhalational anesthesia with isoflurane.

Analysis of myocardial cryosections after modeling of acute pericarditis in mice. To evaluate the manifestations of acute pericarditis, murine hearts were extracted, washed with physiological solution, embedded in Tissue-Tek O.C.T. Compound Medium (Sakura Finetek), frozen in liquid nitrogen vapor, and used to prepare cryosections. Cryosections (7 µm thick) were placed on slides and stored at –70°C Heart sections were stained with hematoxylin-eosin and Mallory's method according to previously described protocols [15–18]. The following solutions were used for Mallory staining: solution A (1% acid fuchsin), B (1% phosphomolybdic acid), and C (2% orange G, 0.5% methyl blue, 2% oxalic acid). Fixed cryosections were sequentially incubated in solution A (2 min), solution B (4 min), and solution C (15 min). Between each staining, the slides were washed with distilled water, dehydrated, and mounted with xylene-based medium.

Immunofluorescence staining was performed using antibodies against markers of activated epicardium Wt1 (Abcam, USA), CD68 macrophages (Abcam, USA), autophagy LC3B (Abclonal, China; Millipore, Germany), and secondary antibodies conjugated to the fluorescent dyes Alexa Fluor 488, Alexa Fluor 594.

Morphometry was performed by manual counting using Image J software (National Institutes of Health, USA).

Evaluation of LC3 expression by immunoblotting. For the analysis of autophagy activity, we used samples of epicardial scrapings from the hearts of control animals and mice after modeling acute pericarditis. Proteins were separated by DSN electrophoresis in 10% polyacrylamide gel on a Mini-PROTEAN 2 device (Bio-rad, USA) and electrotransferred to PVDF membrane (Millipore, USA) on a Trans-blot Turbo device (Bio-rad, USA). After electrotransfer, the membrane was incubated in a blocking buffer (phosphate-buffered saline containing 5% skim milk powder (AppliChem, USA)). The membrane was then incubated with antibodies against LC3 I/II (Abclonal, USA) for 12 hours at +4°C with constant stirring. The membrane was then washed three times in PBS containing 0.05% Tween-20 (each wash for 10 minutes with continuous agitation). After the washes, the membrane was incubated with secondary antibodies against rabbit immunoglobulins conjugated to AffiniPure (H+L) horseradish peroxidase (HRP) (Jackson ImmunoResearch, USA). The membranes were then washed 3 times for 10 minutes each in phosphate-buffered saline containing 0.05% Tween-20. Proteins were detected using SuperSignal West Pico chemiluminescent substrate (Thermo Scientific, USA). The signal was captured using a Fusion-SL 3500.WL gel documentation system (Vilber Lourmat, France). Morphometry was performed using Image J software (National Institutes of Health, USA).

Microscopy and image analysis. Myocardial cell structures and cryosections were analyzed using an Axiovert 200 M fluorescence microscope (Carl Zeiss, USA) and AxioVision 4.8 software (Carl Zeiss, USA).

Statistical significance of differences between samples was evaluated using the non-parametric Mann–Whitney test. Data were analyzed using Statistica 8.0 software (StatSoft, Inc.).

Results

Intrapericardial injection of Freund's adjuvant resulted in the development of signs of acute pericarditis. Intrapericardial injection of Freund's adjuvant into the pericardial cavity induced an inflammatory response in the pericardial leaflets. On day 3 of observation, the acute inflammatory response was manifested by exudation and infiltration with polymorphic cells, including lymphocytes, monocytes, and plasmocytes.

Macroscopically, thickening of pericardial leaflets with loss of transparency and development of adhesions with pleura, diaphragm and lungs was observed on day 5 after inducer administration. Hematoxylin and eosin staining results showed that sham-operated animals showed no signs of morphological changes in the epicardial layer of the heart and did not express Wt1 marker in the epicardial zone. Meanwhile, the visceral pericardium (epicardium) of the experimental group mice was significantly thicker (Fig. 1, *a*, *b*) than the epicardium of the control group animals injected with PBS.

The percentage of thickened epicardial zone in control (after PBS administration) and after Freund's adjuvant administration was 68±9% and 124±22%, respectively (N=6, P=0.009). Wt1+ cells of activated epicardial mesothelium, reorganization of the epicardial/subepicardial area and collagen accumulation were detected (Fig. 2, *c*, *d*), which was practically absent in the control group.

The development of fibrotic transformation of the pericardial leaflet is accompanied by the activation of autophagy in epicardial cells.

Numerous studies show that inflammatory and fibrotic changes in various body tissues are associated with autophagy dysregulation.

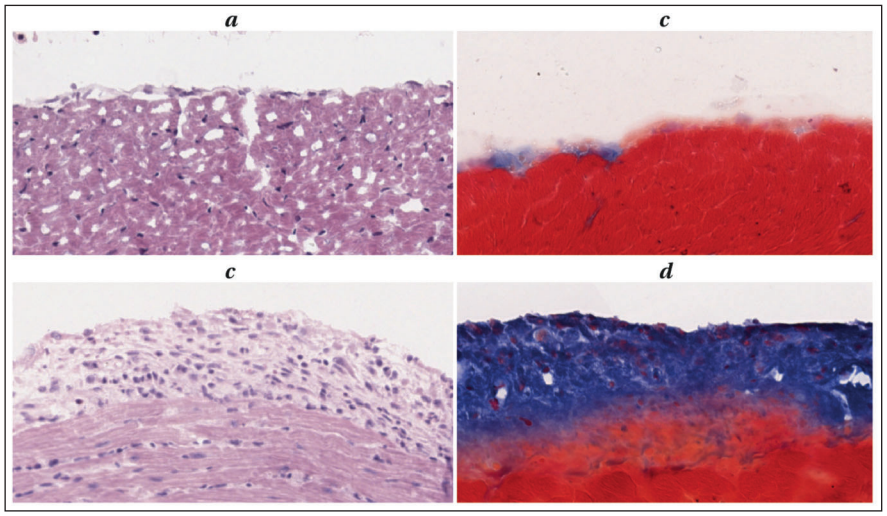

Fig. 1. Morphological changes in the epicardial/subepicardial area after modeling of acute pericarditis (day 5).
Notes. Sections of murine hearts stained: *a, b* — with hematoxylin-eosin; *c, d* — by Mallory method. *a, c* — control group; *b, d* — after acute pericarditis modeling. Blue staining indicates the presence of collagen.

Considering these data, we analyzed autophagy activity after modeling acute pericarditis. LC3 II expression was found to be significantly increased in cells of the activated epicardial layer after adjuvant administration (Fig. 2, *b*) compared to that in control group mice (after PBS administration) (Fig. 2, *a*).

Immunoblotting results showed (Fig. 2, *c*) that during the development of pericarditis, epicardial cells exhibited an 11-fold increase in the ratio of LC3 II / LC3 I (0.07±0.02 in controls and 0.84±0.07 in acute pericarditis groups, P=0.04), indicating increased autophagosome formation and autophagy activity.

Discussion

Currently, pericarditis remains a rather rare disease, which causes significant diagnostic difficulties for primary care physicians [19, 20]. At the same time, even in the case of successful diagnosis, medical treatment has limited efficacy, is often prescribed without considering the etiology, has no effect on the progression of fibrosis in the pericardial leaflets and long-term prognosis. This is largely due to the limited understanding of the cellular mechanisms of pericarditis development and the lack of relevant animal models in the study of the disease [21].

For the first time, our modeling of acute pericarditis in mice showed the following.

1) Intrapericardial Freund's adjuvant injection resulted in an acute inflammatory reaction in the pericardium with thickening and fibrous transformation of the visceral pericardial leaflet, as well as the formation of adhesions.

2) The development of acute pericarditis manifestations was accompanied by autophagy activation in epicardial and subepicardial cells.

The injection of Freund's adjuvant into the pericardial cavity resulted in chaotic redistribution of epicardial cells and significant thickening of the visceral pericardial leaflet. These changes are most likely caused by epicardial cells' ability to initiate epithelial-mesenchymal transition (EMT) in response to proinflammatory microenvironment factors, resulting in their cell cycle entry, enhanced migration ability, differentiation into fibroblasts/myofibroblasts, and matrix accumulation [22]. Furthermore, activated epicardium cells accumulated LC3 II protein involved in autophagosome assembly, indicating autophagy

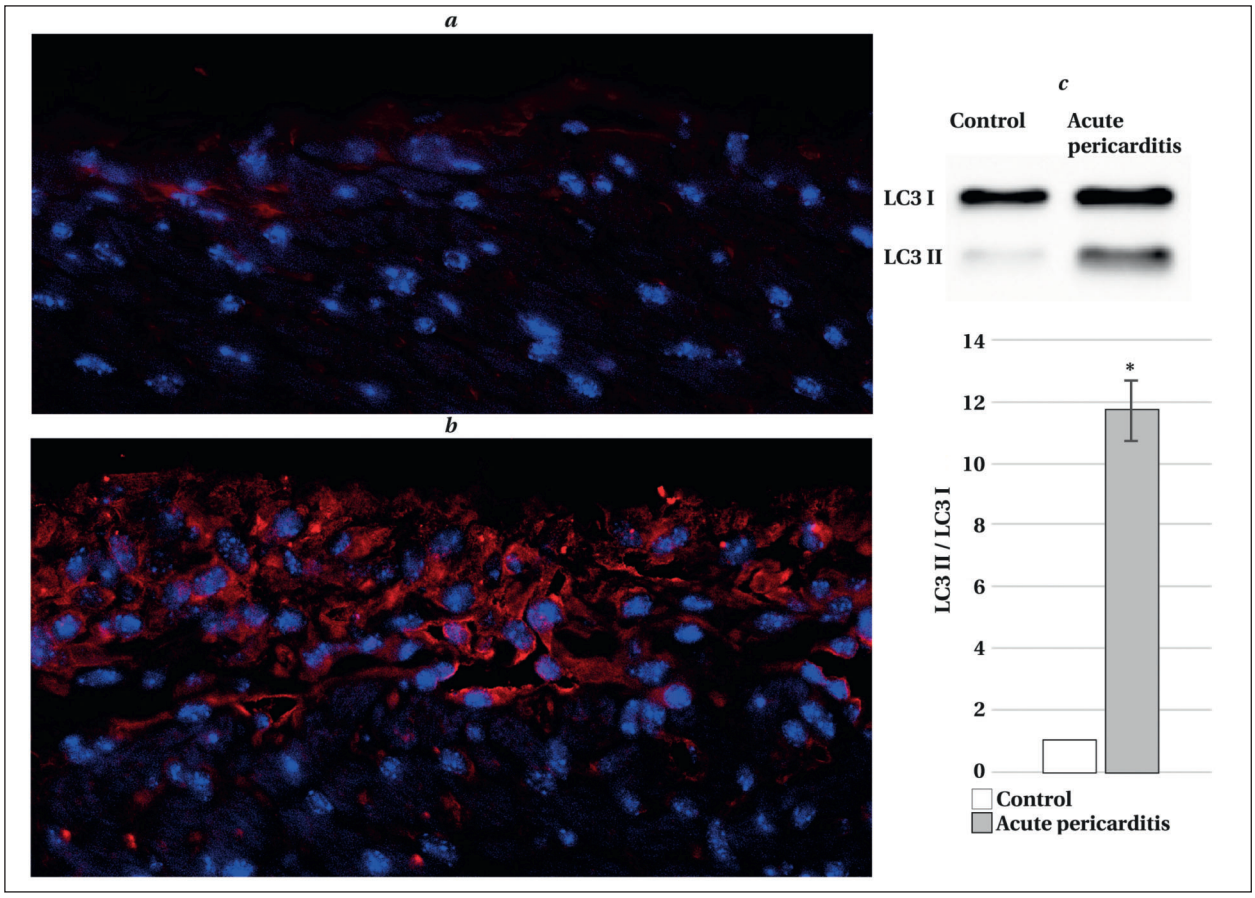

Fig. 2. Development of acute pericarditis induces increased expression of the autophagy marker LC3 in epicardial cells of the murine heart.

Note. Red color *(a, b)* indicates staining of autophagy marker LC3 II. *a* — control group (after FSB injection); *b* — after induction of acute pericarditis. *c* — evaluation of autophagy marker LC3 I and LC3 II expression by immunoblotting and graph. The ratio of LC3 II/LC3 I in the control was taken as 1. * *P*=0.04. Data are shown on day 5 after surgery.

activation, which is a highly conserved process aimed at cell development, differentiation, and adaptation to specialized microenvironmental conditions [23, 24]. These findings are consistent with previous research indicating that autophagy plays an important role in the regulation of the inflammatory response associated with fibrosis [25–27]. High autophagy activity has been linked to the development and maintenance of a proinflammatory microenvironment. Autophagy can regulate the secretion of cytokines like IL-1, IL-18, TNF-α, and IFNγ [28, 29]. Macrophages secrete the mature form of IL-1β in an unconventional manner, relying on chaperone-mediated autophagy that inhibits its secretion in the «baseline» state [30]. The IL-1β secreted by macrophages suppresses the transformation of fibroblasts into myofibroblasts. However, it also stimulates the synthesis of proinflammatory cytokines and matrix metalloproteinases (MMP), promoting inflammation and matrix remodeling [31].

According to the results of recent studies, there is still a strong scientific interest in studying the mechanisms of autophagy involvement in the development of fibrosis in various tissues [32, 33]. However, there is no information on the role of autophagy in the pathogenesis of acute pericarditis or the development of cardiac fibrosis. Meanwhile, the role of autophagy in the formation of myofibroblast pools, which are key players in progressive fibrosis, deserves attention. Suppression of autophagy prevents cardiac fibroblasts from transforming into myofibroblasts, resulting in decreased expression of αSMA and ED-A fibronectin, as well as decreased contractile and migratory activity [34]. In a recent study, autophagy was found to increase collagen I secretion by dermal fibroblasts [35].

Thus, autophagy activation observed during acute pericarditis may be linked to the development of fibrosis in the epicardial zone by promoting a proinflammatory microenvironment, fibroblast/myofibroblast formation, and collagen accumulation. Investigating the possibility of interfering with the progression of epicardial fibrosis by modulating autophagy levels may be a promising area of research for the development of new, highly effective treatments for pericarditis. New Zealand researchers have already taken the first steps in this direction by demonstrating the efficacy of the autophagy in-

hibitor hydroxychloroquine in the treatment of rheumatic pericarditis [36]. Russian researchers [37] confirmed the potential usefulness of hydroxychloroquine by showing that it reduces the severity of inflammation and effusion development in subacute and chronic pericarditis, both alone and in combination with low-dose steroids. According to these findings, autophagy may be a promising therapeutic target for pericardial inflammation.

Conclusion

Acute pericarditis is characterized by activation of epicardial mesothelial cells, increased autophagy activity, and fibrotic changes in the epicardial/subepicardial area.

More research is needed to determine if modulating autophagy can affect the development of acute pericarditis.

References

1. *Лутай Ю. А., Крючкова О. Н., Ицкова Е. А., Турна Э. Ю.* Современные подходы к диагностике и лечению перикардитов. Крымский терапевтический журнал. 2015; 4: 41–45. [*Lutay U. A., Kryuchkova O. N., Itskova E. A., Turna E. U.* Modern approaches to diagnosis and treatment of pericarditis. *Crimean Therapeutic Journal / Krymskiy Terapevticheskiy Zhurnal. 2015*; 4: 41–45. (in Russ.)].
2. *Демин А. А., Дробышева В. П.* Болезни перикарда. Российский кардиологический журнал. 2016; (1): 90–98. [*Dyomin A. A., Drobysheva V. P.* Pericardium diseases. *Russian Journal of Cardiology/ Rossiysky Kardiologichesky Zhurnal.* 2016; (1): 90–98. (in Russ.)]. DOI: 10.15829/1560-4071-2016-1-90-98.
3. *Adler Y., Charron P., Imazio M., Badano L., Barón-Esquivias G., Bogaert J., Brucato A., et al.* 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the diagnosis and management of pericardial diseases of the European Society of Cardiology (ESC) endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2015; 36 (42): 2921–2964. DOI: 10.1093/eurheartj/ehv318. PMID: 26320112.
4. *Косоногов А. Я., Немирова С. В., Поздышев В. И., Никольский А. В., Косоногов К. А., Рыбинский А. Д., Сидоров М. А., с соавт.* Жизнеугрожающие состояния при перикардитах различной этиологии: диагностика и лечение. *Медицинский альманах.* 2019; 2 (59): 40–45. [*Kosonogov A. Ya., Nemirova S. V., Pozdishev V. I., Nikolskiy A. B., Kosonogov K. A., Rybincky A. D., Sidorov M. A., et al.* Life-threatening conditions in pericarditis of different etiologies: diagnosis and treatment. *Medical Almanac/ Meditsinsky Almanah.* 2019; 2 (59): 40–45. (in Russ.)]. DOI: 10.21145/2499-9954-2019-2-40-45.
5. *He Y., Sawalha A. H.* Drug-induced lupus erythematosus: an update on drugs and mechanisms. *Curr Opin Rheumatol.* 2018; 30 (5): 490–497. DOI: 10.1097/BOR. 0000000000000522. PMID: 29870500.
6. *Zipes D. P., Libby P., Bonow R. O., Mann D. L., Braunwald E., Tomaselli G. F.* Braunwald's Heart disease: a textbook of cardiovascular medicine. Elsevier; 2019. https://books. google.ru/books?id=CJyjzQEACAAJ.
7. *Imazio M., Gaita F.* Diagnosis and treatment of pericarditis. *Heart.* 2015; 101 (14): 1159–1168. DOI: 10.1136/HEARTJNL-2014-306362. PMID: 25855795.
8. *Козлов И. А., Овезов А. М., Петровская Э. Л.* Периоперационные повреждение миокарда и сердечная недостаточность в некардиальной хирургии (обзор). Часть 1. Этиопатогенез и прогнозирование периоперационных кардиальных осложнений. *Obshchaya Reanimatologiya = General Reanimatology.* 2019; 15 (2): 53–78.[*Kozlov I. A., Ovezov A. M., Petrovskaya E. L.* Perioperative myocardial damage and heart failure in non-cardiac surgery. Part 1. Etiopathogenesis and prognosis of perioperative cardiac complications (review). *General Reanimatology/Obshchaya Reanimatologya.* 2019; 15 (2): 53–78. (in Russ&Eng.)]. DOI: 10.15360/1813-9779-2019-2-53-78.
9. *Козлов И. А., Овезов А. М., Петровская Э. Л.* Периоперационное повреждение миокарда и сердечная недостаточностьв некардиальной хирургии (обзор). Часть 2. Снижение риска периоперационных кардиальных осложнений с помощью фармакологических мер и оптимизации анестезиолого-реаниматологического обеспечения. *Obshchaya Reanimatologiya = General Reanimatology.* 2019; 15 (3): 83–101. [*Kozlov I. A., Ovezov A. M., Petrovskaya E. L.* Perioperative myocardial damage and heart failure in non-cardiac surgery Part 2. Reduction of the risk of perioperative cardiac complications by pharmacological measures and optimization of anesthetic and critical care support. (review). *General Reanimatology/Obshchaya Reanimatologya.* 2019; 15 (3): 83–101. (in Russ&Eng.)]. DOI: 10.15360/1813-9779-2019-3-83-101.
10. *Григорьев Е. В., Шукевич Д. Л., Плотников Г. П., Кудрявцев А. Н., Радивилко А. С.* Неудачи интенсивного лечения полиорганной недостаточности: патофизиология и потребность в персонификации (обзор литературы). *Вестник интенсивной терапии имени А. И. Салтанова.* 2019; (2): 48–57. [*Grigoriev E. V., Shukevich D. L., Plotnikov G. P., Kudryavtsev A. N., Radivilko A. S.* Failures of intensive treatment of multiple organ failure: pathophysiology and the need for personification (literature review). *Ann Crit Care /Vestnik Intensivnoy Terapii im AI Saltanova.* 2019; (2): 48–57. (in Russ.)]. DOI: 10.21320/18-474 X-2019–2–48–57.
11. *Deretic V., Klionsky D. J.* Autophagy and inflammation: A special review issue. *Autophagy.* 2018; 14 (2): 179–180. DOI: 10.1080/15548627.2017.1412229. PMID: 29304718.
12. *Qian M., Fang X., Wang X.* Autophagy and inflammation. *Clin Transl Med.* 2017; 6 (1): 24. DOI: 10.1186/s40169-017-0154-5. PMID: 28748360.
13. *Yamamoto H., Zhang S., Mizushima N.* Autophagy genes in biology and disease. *Nat Rev Genet.* 2023; 24 (6): 382–400. DOI: 10.1038/S41576-022-00562-W. PMID: 36635405.
14. *Vargas J. N. S., Hamasaki M., Kawabata T., Youle R. J., Yoshimori T.* The mechanisms and roles of selective autophagy in mammals. *Nat Rev Mol Cell Biol.* 2023; 24 (3): 167–185. DOI: 10.1038/s41580-022-00542-2. PMID: 36302887.
15. *Богданов Л. А., Шишкова Д. К., Кутихин А. Г.* Сравнение различных видов прогрессивных гематоксилинов при окрашивании элементов системы кровообращения и гепатолиенальной системы. *Сибирский научный медицинский журнал.* 2019; 39 (6): 46–54.[*Bogdanov L. A., Shishkova D. K., Kutikhin A. G.* Different progressive hematoxylin stains for histological examination of myocardium, blood vessels, liver and spleen. *Siberian Scientific Medical Journal/ Sibirskiy Nauchnyy Meditsinskiy Zhurnal.* 2019; 39 (6): 46–54. In Russ.)]. DOI: 10.15372/SSMJ20190606.
16. *Dergilev K. V., Makarevich P. I., Tsokolaeva Z. I., Boldyreva M. A., Beloglazova I. B., Zubkova E. S., Menshikov M. Y., et al.* Comparison of cardiac stem cell sheets detached by Versene solution and from thermoresponsive dishes reveals similar properties of constructs. *Tissue Cell.* 2017; 49 (1): 64–71. DOI: 10.1016/j.tice.2016.12.001. PMID: 28041835.
17. *Дергилев К. В., Цоколаева З. И., Рыжков И. А., Парфенова Е. В.* Трансплантация пластов мезенхималь-

ных прогениторных клеток сердца для васкуляризации миокарда после инфаркта. *Obshchaya Reanimatologiya = General Reanimatology.* 2018; 14 (6): 28–40. [*Dergilev K. V., Tsokolaeva Z. I., Ryzhkov I. A., Parfenova E. V.* Transplantation of cardiac mesenchymal progenitor cell sheets for myocardial vascularization after an infarction. *General Reanimatology/Obshchaya Reanimatologya.* 2018; 14 (6): 28–40. (in Russ&Eng.)]. DOI: 10.15360/1813-9779-2018-6-28-40.

18. *Дергилев К. В., Цоколаева З. И., Василец Ю. Д., Белоглазова И. Б., Парфенова Е. В.* Клеточные пласты на основе кардиальных прогениторных клеток продуцируют проангиогенные факторы роста и оказывают локальное стимулирующее воздействие на формирование капилляров после инфаркта миокарда. *Комплексные проблемы сердечно-сосудистых заболеваний.* 2021; 10 (3): 34–43. [*Dergilev K. V., Tsokolaeva Z. I., Vasilets Yu. D., Beloglazova I. B., Parfenova E. V.* Cardiac progenitor cell sheets secrete proangiogenic growth factors and locally activate capillarogenesis after infarction. *Complex Issues of Cardiovascular Diseases/Kompleksnye Problemy Serdechno-Sosudistykh Zabolevany.* 2021; 10 (3): 34–43. (in Russ.)]. DOI: 10.17802/2306-1278-2021-10-3-34-43.
19. *Shahid R., Jin J., Hope K., Tunuguntla H., Amdani S.* Pediatric pericarditis: update. *Curr Cardiol Rep.* 2023; 25 (3): 157–170. DOI: 10.1007/s11886-023-01839-0. PMID: 36749541.
20. *Mohan T., Tressa J. M., Ushasree P., Tharani P., Muzaffar A.* Myocarditis and pericarditis. *Innov Technol Sci Educ.* 2023; 2 (9): 1885–1896.
21. *Kosmopoulos M., Liatsou E., Theochari C., Stavropoulos A., Chatzopoulou D., Mylonas K. S., Georgiopoulos G., et al.* Updates on the global prevalence and etiology of constrictive pericarditis: a systematic review. *Cardiol Rev.* 2023. DOI: 10.1097/CRD.0000000000000529. PMID: 36883817.
22. *Li J., Takasato M., Xu Q., Bijkerk R.* Editorial: epithelial plasticity and complexity in development, disease and regeneration. *Front Cell Dev Biol.* 2023; 10: 1105402. DOI: 10.3389/fcell. 2022.1105402. PMID: 36712966.
23. *Popov S. V., Mukhomedzyanov A. V., Voronkov N. S., Derkachev I. A., Boshchenko A. A., Fu F., Sufianova G. Z., et al.* Regulation of autophagy of the heart in ischemia and reperfusion. *Apoptosis.* 2023; 28 (1–2): 55–80. DOI: 10.1007/s10495-022-01786-1.PMID: 36369366.
24. *Wang Y., Gao J., Fan B., Hu Y., Yang Y., Wu Y., Li F., et al.* Different levels of autophagy induced by transient serum starvation regulate metabolism and differentiation of porcine skeletal muscle satellite cells. *Sci Rep.* 2023; 13 (1): 13153. DOI: 10.1038/S41598-023-40350-Y. PMID: 37573414.
25. *Ruby M., Gifford C. C., Pandey R. P., Raj V. S., Sabbisetti V. S., Ajay A. K.* Autophagy as a therapeutic target for chronic kidney disease and the roles of TGF-β1 in autophagy and kidney fibrosis. *Cells.* 2023; 12 (3): 412. DOI: 10.3390/ cells12030412. PMID: 36766754.
26. *Macias-Ceja D. C., Barrachina M. D., Ortiz-Masià D.* Autophagy in intestinal fibrosis: relevance in inflammatory bowel disease. *Front Pharmacol.* 2023; 14: 1170436. DOI: 10.3389/fphar.2023. 1170436. PMID: 37397491.
27. *Su H. Y., Yang J. J., Zou R., An N., Chen X.-C., Yang C., Yang H.-J., et al.* Autophagy in peritoneal fibrosis. *Front Physiol.* 2023; 14: 1187207. DOI: 10.3389/fphys. 2023. 1187207. PMID: 37256065.
28. *Weigert A., Herhaus L.* Immune modulation through secretory autophagy. *J Cell Biochem.* Published online 2023. DOI: 10.1002/jcb.30427. PMID: 37260061.
29. *Zuo H., Chen C., Sa Y.* Therapeutic potential of autophagy in immunity and inflammation: current and future perspectives. *Pharmacol Reports.* 2023; 75 (3): 499–510. DOI: 10.1007/s43440-023-00486-0. PMID: 37119445.
30. *Dupont N., Jiang S., Pilli M., Ornatowski W., Bhattacharya D., Deretic V.* Autophagy-based unconventional secretory pathway for extracellular delivery of IL-1β. *EMBO J.* 2011; 30 (23): 4701–4711. DOI: 10.1038/emboj.2011.398. PMID: 22068051.
31. *Frangogiannis N. G.* Interleukin-1 in cardiac injury, repair, and remodeling: pathophysiologic and translational concepts. *Discoveries.* 2015; 3 (1): e41. DOI: 10.15190/d.2015.33. PMID: 26273700.
32. *Wen J.-H., Li D.-Y., Liang S., Yang C., Tang J.-X., Liu H.-F.* Macrophage autophagy in macrophage polarization, chronic inflammation and organ fibrosis. *Front Immunol.* 2022; 13: 946832. DOI: 10.3389/fimmu. 2022.946832. PMID: 36275654.
33. *Dai R., Zhang L., Jin H., Wang D., Cheng M., Sang T., Peng C., et al.* Autophagy in renal fibrosis: protection or promotion? *Front Pharmacol.* 2022; 13: 963920. DOI: 10.3389/fphar.2022. 963920. PMID: 36105212.
34. *Gupta S. S., Zeglinski M. R., Rattan S. G., Landry N. M., Ghavami S., Wigle J. T., Klonisch T., et al.* Inhibition of autophagy inhibits the conversion of cardiac fibroblasts to cardiac myofibroblasts. *Oncotarget.* 2016; 7 (48): 78516–78531. DOI: 10.18632/ONCOTARGET.12392. PMID: 27705938.
35. *Nakamura T., Yamashita M., Ikegami K., Suzuki M., Yanagita M., Kitagaki J., Kitamura M., et al.* Autophagy facilitates type I collagen synthesis in periodontal ligament cells. *Sci Rep.* 2021; 11 (1): 1291. DOI: 10.1038/ s41598-020-80275-4. PMID: 33446772.
36. *Wilson N. J., Concannon A., Malcolm J., Davidakova S., Martin W. J., Webb R., Moreland N. J.* The Treatment of acute rheumatic fever: novel use of hydroxychloroquine. *Pediatr Infect Dis J.* 2020; 39 (7): e120-e122. DOI: 10.1097/INF.000000 0000002647. PMID: 32221169.
37. *Благова О. В., Сорокин Г. Ю., Седов В. П., Коган Е. А., Саркисова Н. Д., Недоступ А. В.* Инфекционно-иммунные перикардиты: оценка клинического спектра, возможности диагностики, дифференцированная базисная терапия с применением гидроксихлорохина. *Российский кардиологический журнал.* 2020; 25 (11): 11–22. [*Blagova O. V., Sorokin G.Yu., Sedov V. P., Kogan E. A., Sarkisova N. D., Nedostup A. V.* Infectious-immune pericarditis: clinical assessment, diagnostic, and differentiated baseline therapy with hydroxychloroquine. *Russian Journal of Cardiology/ Rossiysky Kardiologichesky Zhurnal*; 25 (11): 11–22. (in Russ.)]. DOI: 10.15829/29/1560-4071-2020-3840.

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