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Destabilization of the Organized Structure of Ventricular Fibrillation During Reperfusion

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Summary

Aim: to study the effect of reperfusion on the organized frequency-amplitude structure of ventricular fibrillation (VF) in the dog heart.

Materials and methods. We conducted 4 experiments on 8 dogs. In each experiment, the isolated heart of one dog was perfused with the blood of the second (supporting) dog. In 4 experiments on an isolated artificially perfused heart, 6 episodes of 3 min ischemia and 10 min reperfusion of the heart were performed in VF (1–2 episodes of ischemia-reperfusion in one experiment). Each episode of 3 min ischemia in VF was preceded by a 10 min perfusion of the heart in VF. Ventricular electrogram was recorded during VF episodes. A frequency-amplitude (spectral) analysis of 1 sec segments of the electrogram was performed, and the proportion (in %) of 0.5–15 Hz frequency oscillations in 10 sec segments of the electrogram was determined in 6 episodes of perfusion, ischemia and reperfusion in VF ($M \pm m$, N=60). The VF frequency-amplitude structures during ischemia and reperfusion were compared with the stable VF frequency-amplitude structure during perfusion taken as the control. The nonparametric Welch criterion in the «The R Project for Statistical Computing» software environment was used to compare the VF parameters during perfusion, ischemia and reperfusion.

Results. 9–10 Hz frequency oscillations dominated in the VF frequency-amplitude structure during heart perfusion, taken as the control. In the first 30 sec of ischemia, the frequency and amplitude of the dominant oscillations did not significantly change vs VF control obtained during cardiac perfusion. A decrease of dominant oscillations frequency up to 6.5–7.5 Hz, and of the proportion of oscillations — up to 26% was documented at the 3rd min of ischemia. At the 1st min of reperfusion, the frequency of dominant oscillations increased to 13.5–14.5 Hz, but the proportion of oscillations remained reduced to 26%, as at the 3rd min of ischemia. At the 2nd min of reperfusion, the frequency of dominant oscillations decreased to 9.5–10.5 Hz, and the proportion of dominant oscillations increased to 33%. The frequency and amplitude of the dominant oscillations stabilized at 3–10 min of reperfusion: oscillations at 9–10 Hz frequency accounted for 32–33% of the spectral power.

Conclusion. Reperfusion in VF is characterized by transient destabilization of VF organized structure at the 1st min of the procedure. VF organized structure regains stabilization within 2–10 min of reperfusion. Cardiac perfusion in intentionally induced VF can be used instead of cardioplegia during major cardiac surgery to boost cardiac resistance to ischemia and prevent or reduce reperfusion complications.

Keywords: ventricular fibrillation; cardiac perfusion; cardiac ischemia; cardiac reperfusion; organized frequency-amplitude structure of fibrillation

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

Introduction

Ventricular fibrillation (VF) is a fatal cardiac arrhythmia and the most frequent cause of sudden cardiac death, which is the leading cause of mortality in many countries, including Russia [1, 2], and therefore remains an urgent problem. VF is considered to be a turbulent process [3, 4], in which, however, organized activity has been revealed both in mapping, reflecting local activity in VF [5, 6], and in electrocardiogram analysis, reflecting global VF activity [7].

We have shown that VF is characterized by stable organized activity during perfusion of the canine heart, which is confirmed by the dominance of 9–10 Hz oscillations, which are only 1/10 of the frequency range of 0.5–15 Hz, but contain more than 1/3 of the spectral power [8]. The frequency and amplitude parameters of the canine VF are applicable to humans because the frequency of the canine VF is close to that of the human VF [9].

In VF under cardiac ischemia, organized VF activity decreases along with the chances of successful defibrillation [5–7]. Therefore, restoration of myocardial perfusion is a prerequisite for restoration of cardiac rhythm during defibrillation. Organized VF activity, reduced by ischemia, should be restored during cardiac reperfusion, which would increase the chances of successful defibrillation.

However, myocardial reperfusion is associated with complications, including arrhythmias [10]. Therefore, VF may also be associated with reperfusion complications, including destabilization of the organized frequency and amplitude structure of VF.

Although VF and reperfusion are relevant issues, few studies have been devoted to the investigation of VF during reperfusion. In an isolated perfused heart from patients with cardiomyopathy who underwent donor heart transplantation, the dominant VF frequency decreased from 4.9 to 3.6 Hz during 200 sec of ischemia and increased to 4.7 Hz during 120 sec of reperfusion [11]. However, the functional activity of a nonviable (donor-replaced) heart cannot reflect the activity of a viable heart.

In VF induced during cardiac surgery, the dominant VF frequency increased from 5.3 to 6.4 Hz during 30 sec of perfusion, decreased to 4.7 Hz during 150 sec of ischemia, and increased to 7.1 Hz during 30 sec of reperfusion [12]. The reperfusion interval was reported to be shorter than the ischemia interval [11, 12], which we believe is insufficient to restore the organized frequency and amplitude structure of the VF during reperfusion. The dominant frequency of VF during perfusion used to compare changes in VF during ischemia and reperfusion was not specified[11], whereas in another study the dominant frequency of VF during the 30 sec perfusion before ischemia was variable during VF[12]. In addition, it is unclear how to characterize the frequency and amplitude structure of VF using a single, albeit dominant, VF frequency.

Thus, reperfusion complications of VF, including destabilization of the organized frequency and amplitude structure of VF during reperfusion, have not been clarified [11, 12]. Destabilization of the organized structure of VF during reperfusion may reduce the chances of successful defibrillation.

The aim of this study was to investigate the effect of reperfusion on the organized frequency and amplitude structure of VF in the canine heart.

Materials and methods

We performed 4 experiments on 8 mongrel dogs of both sexes weighing 20–30 kg according to the recommendations of the International Committee for Laboratory Animals, supported by the WHO, European Parliament Directive No. 2010/63/EU of 22.09.2010 «On the protection of animals used for scientific purposes».

Premedication was performed with subcutaneous atropine sulfate 0.1 mg/kg, followed 10 min later by intramuscular Zoletil® (Zolazepam hydrochloride 20–30 mg/kg (VIRBAC S.A., France). Five to 10 min after Zoletil® administration, the dog was placed on the operating table. Under intravenous thiopental anesthesia (10–15 mg/kg initial dose and 4–7 mg/kg hourly), mechanical ventilation was started and the heart was isolated from the thorax. The aorta was cannulated and the coronary arteries were perfused with the cardioplegic solution Custodiol® (Dr. F. Köhler Chemie GmbH, Germany). Supportive cardiac perfusion was then started with blood from another dog ventilated under thiopental anesthesia. The interval between cardioplegia and initiation of supportive perfusion did not exceed 10 min. Ischemia is known to be reversible without damage to cardiac structure and function when perfusion is initiated within 10 min of cardioplegia [13]. Arterial blood was supplied to the aorta of the isolated heart from the femoral artery of the supporting dog. The perfusion pressure in the aorta was 90–100 mmHg, resulting in aortic valve closure and retrograde perfusion of the coronary arteries with blood from the supporting dog. Venous blood from the atria of the isolated heart was returned to the femoral vein of the supporting dog. Heparin (500 IU/kg initially and 150 IU/kg hourly) was administered to prevent thrombosis. The heart was maintained in an enclosed chamber at 37°C.

In 4 experiments, 6 episodes of 3 min ischemia and 10 min reperfusion of the heart during VF were performed on an isolated perfused heart (1–2 episodes of ischemia-reperfusion per experiment). Each episode of 3 min of ischemia in VF was preceded by 10 min of cardiac perfusion in VF.

A clamp was placed on the aortic tube feeding the isolated heart to obtain ischemia during VF, and removal of the clamp resulted in reperfusion during VF.

Ventricular electrograms during perfusion, ischemia, and reperfusion of the heart during VF were recorded with bipolar electrodes in the right and left ventricles on a Cardiotechnica-EKG-8 cardiograph (Inkart, St. Petersburg) at a digitizing frequency of 1000 Hz.

Ventricular fibrillation was induced by frequent electrical stimulation of the heart through bipolar electrodes in the apex of the left ventricle. No pre-VF electrogram abnormalities were detected.

Frequency and amplitude (spectral) analysis of electrograms during perfusion, ischemia, and reperfusion of the heart in VF was performed using the Fast Fourier Transform method in the frequency range of 0.5–15 Hz, which is the best method for determining the spectral parameters of VF [14].

The spectral analysis of 1 sec electrogram segments was performed and the proportion (%) of 0.5–15 Hz oscillations in 10 sec electrogram segments was determined in 6 episodes of perfusion, ischemia, and reperfusion during VF ($M \pm m$, N=60). The stable frequency and amplitude structure of VF during perfusion served as a reliable control for comparing the spectral structure of VF during ischemia and reperfusion.

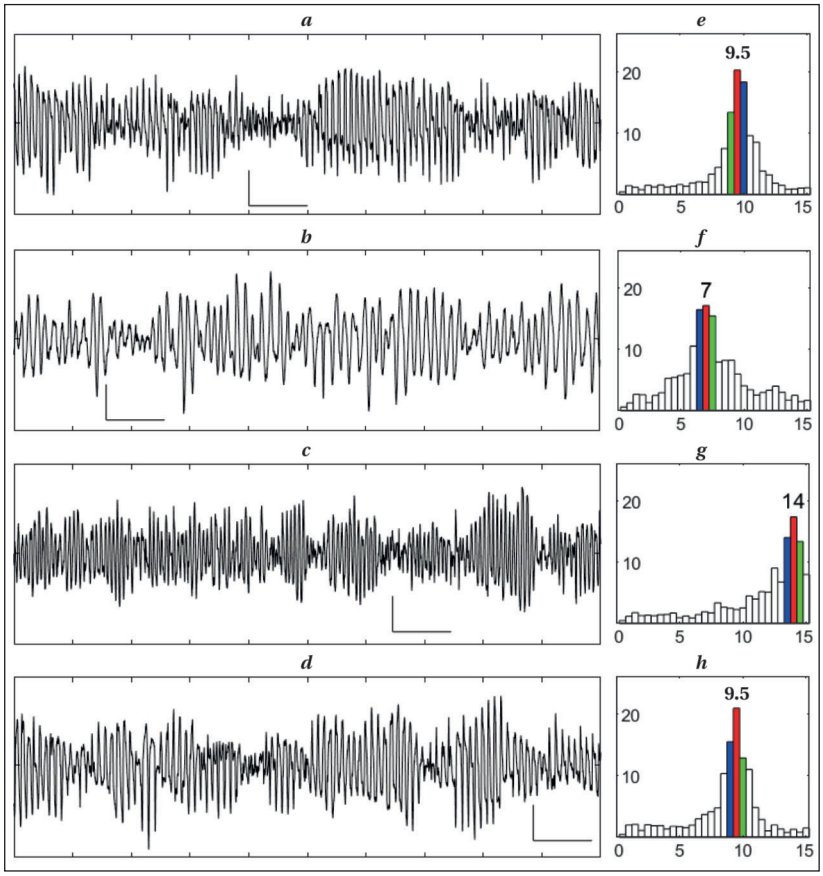

Fig. 1. Cardiac electrograms of the dog.
Note. *(a)* during perfusion; *(b)* at 171–180 sec of ischemia; *(c), (d)* at 51–60 and 581–590 sec of reperfusion of the heart in VF, respectively; *(e)–(h)* spectrograms of electrograms. Calibration of electrograms: 2 mV; 1 sec. Spectrograms: horizontal axis — frequency, Hz; vertical axis — amplitude, mV.

The ventricular fibrillation parameters during perfusion, ischemia, and reperfusion were compared by the nonparametric Welch criterion using R Project for Statistical Computing [15].

Differences at $P<0.05$ were considered significant.

Results

Oscillations of 9–10 Hz frequency dominated the electrogram and spectrogram during cardiac perfusion in VF (Fig. 1, *a, e*).

Oscillations of 6.5–7.5 Hz frequency were dominant at 3 min of ischemia during VF (Fig. 1, *b, f*). Oscillations of 13.5–14.5 Hz were dominant at the 1st min of reperfusion (Fig. 1, *c, g*), and oscillations of 9–10 Hz were dominant at the 10th min of reperfusion in VF (Fig. 1, *d, h*).

The dominant spectral structure on electrograms and spectrograms during ischemia and reperfusion of the heart in VF (Fig. 1) is shown in Fig. 2. During cardiac perfusion in VF, which served as a control, oscillations of 9–10 Hz frequency accounted for 32% of the spectral power and dominated the frequency and amplitude structure of VF (Fig. 2, *a*).

During the first 30 sec of ischemia, the frequency and amplitude of dominant VF oscillations did not change significantly (P=0.08) compared to the control during cardiac perfusion in VF (Fig. 1, *b*). At 3 min of ischemia, the frequency of dominant VF oscillations decreased to 6.5–7.5 Hz (P=0.001) and the proportion of dominant oscillations decreased to 26% (P=0.005) (Fig. 2, *c*), indicating a 20% decrease in proportion compared to the control during cardiac perfusion in VF.

At 1 min of reperfusion, the frequency of dominant VF oscillations increased to 13.5–14.5 Hz (P=0.001), while the proportion of dominant oscillations remained reduced to 26%, as at 3 min of ischemia (Fig. 2, *d*). At 2 min of reperfusion, the frequency of dominant oscillations decreased to 9.5–10.5 Hz (P=0.002), while the proportion of dominant oscillations increased to 33% (P=0.001) (Fig. 2, *e*).

At 3–10 min of reperfusion, the frequency amplitude of the dominant oscillations of the VF stabilized, i. e., oscillations of 9–10 Hz frequency accounted for 32–33% of the spectral power (Fig. 2, *f, g*).

Discussion

The dominant frequency and amplitude structure of VF during ischemia and reperfusion in VF was demonstrated, suggesting organized VF activity. However, the dynamics of VF during ischemia, when ischemia in VF was preceded by cardiac perfusion in VF, differed from those of cardiac VF in situ, when ischemia in VF was preceded by coordinated cardiac contractions. Ventricular fibrillation in situ is characterized by rapid changes during ischemia, as the dominant frequency and organized activity of VF begin to decrease as early as the first 10–15 sec of ischemia in VF [16, 17], and by the third min of ischemia, the dominant frequency of VF decreases by 5–6 Hz, while the organized activity of VF decreases 2-fold [5–7].

The frequency and amplitude structure of VF was stable in the first 30 sec of ischemia in VF, and at 3 min of ischemia, the frequency of dominant oscillations decreased by only 2.5 Hz (Fig. 2). Using the proportion of dominant VF oscillations as a quantitative parameter of organized VF activity, we can conclude that organized VF activity decreased by only 20% at 3 min of ischemia.

These data suggest that cardiac perfusion during VF increases the resistance of the organized spectral structure of VF to ischemia.

Reperfusion after 3 min of ischemia was characterized by a strong transient destabilization of the organized spectral structure of the VF, as confirmed by a 2-fold increase, from 7 to 14 Hz, in the dominant frequencies of the VF and a 20% decrease in organized activity at 1 min of reperfusion in the VF (Fig. 2). At least 2–3 min of VF reperfusion are required to restore and stabilize the frequency and amplitude structure of the VF. In our opinion, transient destabilization of organized activity during the 1st min of reperfusion should be considered a complication of reperfusion because such destabilization may provoke refibrillation during the first 30–60 sec of reperfusion after defibrillation. It can be hypothesized that chest compressions performed for 1 min during CPR destabilize VF activity, which is unfavorable for defibrillation, whereas chest compressions performed for longer periods of 2–3 min stabilize VF activity and improve defibrillation success.

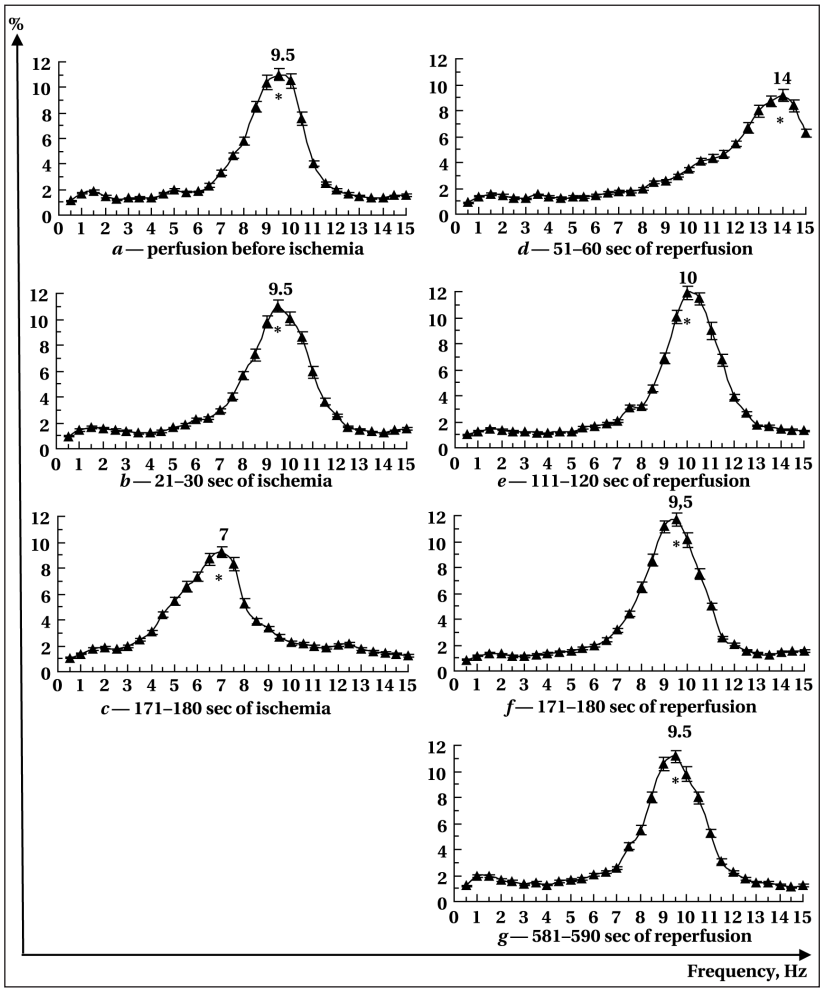

Fig. 2. Proportion of oscillations with frequency 0.5–15 Hz.
Note. *(a)* during perfusion; *(b)* at 1–3 min of ischemia; *(c)–(g)* at 1–10 min of reperfusion of the dog heart in ventricular fibrillation. Data are expressed as M±m, N=60. * $P<0.01$ when the three frequencies with the highest specific gravity were compared with the other frequencies.

Apparently, the organized structure of the VF becomes more resistant to ischemia after perfusion during VF because of the increase in ATP in the myocardium during perfusion during VF, as 10 times less energy is expended during VF than during coordinated contractions [13].

The increase in oscillation frequency at 1 min of reperfusion in VF indicates an increase in ATP synthesis, which suggests an acceleration of oxidative phosphorylation reactions and an increase in electron flow through the mitochondrial respiratory chain [18, 19]. However, the throughput of the respiratory chain is limited, and a pulse increase in the flow of high-energy electrons may lead to a slowing of the electron flow through the respiratory chain during reperfusion, which could cause thermal damage to the iron-sulfur centers and cytochromes of the respiratory chain. Damage to coenzymes of the respiratory chain can be considered the basis of in situ reperfusion injury of the heart, and increased permeability of the mitochondrial inner membrane and other mechanisms of myocardial reperfusion injury [20, 21] are the consequences of a primary alteration of the mitochondrial respiratory chain in the first 30–60 sec of reperfusion.

Based on our findings, we suggest that cardiac perfusion with induced VF can be used during prolonged cardiac surgery to increase cardiac resistance to ischemia and prevent reperfusion complications, which would improve the quality of surgery and postoperative cardiac recovery. During cardioplegia, which is used to «maintain» the operated heart, the myocardium still undergoes ischemia and reperfusion [22, 23], and several papers address myocardial protection from ischemia and reperfusion during cardioplegia [24, 25].

The issue of cardiac perfusion in induced VF during cardiac surgery needs further investigation. Our results were obtained in the isolated canine heart perfused with the blood of the supporting dog, whereas in the cardiac surgery clinic the human heart is perfused in situ with cardiopulmonary bypass and membrane oxygenator.

The limitation of the study was the lack of a control group with the same observation period but without ischemia-reperfusion. Cardiac electro-

grams obtained at a baseline (before ischemia-reperfusion) served as a control in the experiment. The baseline VF values represent generally accepted control for studying VF during ischemia and reperfusion [5, 6, 11, 12].

Hundreds of parasympathetic ganglia and tens of thousands of neurons affecting cardiac rhythm and conduction are localized around the sinus and atrial-ventricular node [26]. Nervous tissue is sensitive to ischemia and reperfusion [27], and ischemic and reperfusion injury to cardiac nervous tissue during cardioplegia can cause cardiac rhythm and conduction disturbances.

Perfusion of the operated heart instead of cardioplegia in induced VF may protect both myocardium and cardiac nervous tissue.

Conclusion

A transient destabilization of the organized structure of VF during the 1st min of reperfusion is typical of reperfusion in VF. The organized structure of VF becomes stable at 2–10 min of reperfusion. The use of cardiac perfusion instead of cardioplegia for induced VF during prolonged cardiac surgery could increase the resistance of the operated heart to ischemia and prevent reperfusion complications.

References

1. *Лебедев Д.С., Михайлов Е.Н., Неминущий Н.М., Голухова Е.З., Бабокин В.Е. Березницкая В.В., Васичкина Е.С., и др.* Желудочковые нарушения ритма. Желудочковые тахикардии и внезапная сердечная смерть. Клинические рекомендации 2020. *Российский кардиологический журнал.* 2021; 26 (7): 128–189. [*Lebedev D.S., Mikhailov E.N., Neminuschiy N.M., Golukhova E.Z., Babokin V.E., Bereznitskaya V.V., Vasichkina E.S., et al.*Ventricular arrhythmias. Ventricular tachycardias and sudden cardiac death. 2020 Clinical guidelines. *Russian Journal of Cardiology/ Rossiysky Kardiologichesky Zhurnal.* 2021; 26 (7): 128–189. (In Russ.)]. DOI: 10.15829/1560-4071-2021-4600.
2. *Narayan S.M., Wang P.J., Daubert J.P.* New concepts in sudden cardiac arrest to address an intractable epidemic: JACC state-of-the-art review. *J Am Coll Cardiol.* 2019; 73 (1): 70–88. DOI: 10.1016/j.jacc.2018.09.083.
3. *Jenkins E.V., Dharmaprani D., Schopp M., Quah J.X., Tiver K., Mitchell L., Xiong F., et al.* The inspection paradox: An important consideration in the evaluation of rotor lifetimes in cardiac fibrillation. *Front Physiol.* 2022; 13: 920788. DOI: 10.3389/fphys.2022.920788. PMID: 36148313.
4. *Rappel W.-J.* The physics of heart rhythm disorders. *Phys. Rep.* 2022; 978: 1–45. DOI: 10.1016/j.physrep.2022.06.003. PMID: 36843637.
5. *Huang J., Dosdall D.J., Cheng K.-A., Li L., Rogers J.M., Ideker R.E.* The importance of Purkinje activation in long duration ventricular fibrillation. *J Am Heart Assoc.* 2014; 3 (1): e000495. DOI: 10.1161/jaha.113. 000495. PMID: 24584738.
6. *Venable P.W., Taylor T.G., Shibayama J., Warren M., Zaitsev A.V.* Complex structure of electrophysiological gradients emerging during long-duration ventricular fibrillation in the canine heart. *Am J Physiol Heart Circ Physiol.* 2010; 299 (5): H1405–H1418. DOI: 10.1152/ajpheart. 00419.2010. PMID: 20802138.
7. *Гурьянов М.И.* Организованная частотная структура электрокардиограммы при длительном развитии фибрилляции желудочков сердца в эксперименте. *Современные технологии в медицине.* 2016; 8 (3): 37–48. [*Guryanov M.I.* Organized frequency structure of electrocardiogram during long-duration ventricular fibrillation under experimental conditions. *Modern Technologies in Medicine/ Sovrem Tekhnologii Med.* 2016; 8 (3): 37–48. (in Russ.)]. DOI: 10.17691/stm2016.8.3.04.
8. *Гурьянов М.И., Пусев Р.С., Гурьянова Н.М., Харитонова Е.А., Яблонский П.К.* Организованная структура фибрилляции желудочков собаки при перфузии сердца в длительном эксперименте. *Современные технологии в медицине.* 2021; 12 (3): 26–30. [*Guryanov M.I., Pusev R.S., Guryanova N.M., Kharitonova E.A., Yablonsky P.K.* Organized structure of ventricular fibrillation during prolonged heart perfusion in dogs. *Modern Technologies in Medicine/ Sovrem Tekhnologii Med.* 2021; 12 (3): 26–30. (in Russ.)]. DOI: 10.17691/stm2020.12.3.03. PMID: 34795976.
9. *Noujaim S.F., Berenfeld O., Kalifa J., Cerrone M., Nanthakumar K., Atienza F., Moreno J., et al.* Universal scaling law of electrical turbulence in the mammalian heart. *PNAS/Proc Natl Acad Sci USA.* 2007; 104 (52): 20985–20989. DOI: 10.1073/pnas.0709758104. PMID: 18093948.
10. *van der Weg K., Prinzen F.W., Gorgels A.P.* Editor's Choice-Reperfusion cardiac arrhythmias and their relation to reperfusion-induced cell death. *Eur Heart J Acute Cardiovasc Care.* 2019; 8 (2): 142–152. DOI: 10.1177/2048872618812148. PMID: 30421619.
11. *Masse S., Farid T., Dorian P., Umapathy K., Nair K., Asta J., Ross H., et al.* Effect of global ischemia and reperfusion during ventricular fibrillation in myopathic human hearts. *Am J Physiol Heart Circ Physiol.* 2009; 297 (6): H1984–H1991. DOI: 10.1152/ajpheart.00101.2009. PMID: 19820201.
12. *Bradley C.P., Clayton R.H., Nash M.P., Mourad A., Hayward M., Paterson D.J., Taggart P.* Human ventricular fibrillation during global ischemia and reperfusion: paradoxical changes in activation rate and wavefront complexity. *Circ Arrhythm Electrophysiol.* 2011; 4 (5): 684–691. DOI: 10.1161/CIRCEP.110.961284. PMID: 21841193.
13. *Gebhard M.-M., Bretschneider H.J., Schnabel P.A.* Cardioplegia principles and problems. In: Physiology and pathophysiology of the heart. Developments in cardiovascular medicine. vol 90. Springer, Boston, MA; 1989: 655–668. DOI: 10.1007/978-1-4613-0873-7_32.
14. *Oñate B.C.P., Meseguer M.F.-M., Carrera E.V., Muñoz S.J.J., Alberola A.G., Álvarez J.L.R.* Different ventricular fibrillation types in low-dimensional latent spaces. *Sensors (Basel).* 2023 (5); 23; 2527. DOI: 10.3390/s23052527. PMID: 36904731.
15. The R Project for Statistical Computing. https: //www.r-project.org/. Дата обращения 27.04.2023/accessed 27.04.2023.

16. *Haissaguerre M., Cheniti G., Hocini M., Sacher F., Ramirez F.D., Cochet H., Bear L., et al.* Purkinje network and myocardial substrate at the onset of human ventricular fibrillation: implications for catheter ablation. *Eur Heart J.* 2022; 43 (12): 1234–1247. DOI: 10.1093/eurheartj/ehab893. PMID: 35134898.
17. *Meo M., Denis A., Sacher F., Duchâteau J., Cheniti G., Puyo S., Bear L., et al.* Insights into the spatiotemporal patterns of complexity of ventricular fibrillation by multilead analysis of body surface potential maps. *Front Physiol.* 2020; 11: 554838. DOI: 10.3389/fphys.2020.554838. PMID: 33071814.
18. *Marin W., Marin D., Ao X., Liu Y.* Mitochondria as a therapeutic target for cardiac ischemia-reperfusion injury (Review). *Int J Mol Med.* 2021; 47 (2): 485–499. DOI: 10.3892/ijmm.2020.4823. PMID: 33416090.
19. *Nelson D.L., Cox M.M.* Oxidative phosphorylation and photophosphorilation. In: Lehninger principles of biochemistry. W.H. Freeman and Company; 2014: 707–772.
20. *Zhao T., Wu W., Sui L., Huang Q., Nan Y., Liu J., Ai K., et al.* Reactive oxygen species-based nanomaterials for the treatment of myocardial ischemia reperfusion injuries. *Bioact Mater.* 2022; 7: 47–72. DOI: 10.1016/j.bioactmat.2021.06.006. PMID: 34466716.
21. *Davidson S.M., Adameová A., Barile L., Cabrera-Fuentes H.A., Lazou A., Pagliaro P., Stensløkken K.-O., et al.* Mitochondrial and mitochondrial-independent pathways of myocardial cell death during ischaemia and reperfusion injury. *J Cell Mol Med.* 2020; 24 (7): 3795–3806. DOI: 10.1111/jcmm.15127. PMID: 32155321.
22. *Krasniqi L., Ipsen M.H., Schrøder H.D., Hejbøl E.K., Rojek A.M., Kjeldsen B.J., Riber P.* Stone heart syndrome after prolonged cardioplegia induced cardiac arrest in open-heart surgery — a pilot study on pigs. *Cardiovasc Pathol.* 2022; 60: 107427. DOI: 10.1016/j.carpath.2022.107427. PMID: 35436604.
23. *Aass T., Stangeland L., Moen C.A., Solholm A., Dahle G.O., Chambers D.J., Urban M., et al.* Left ventricular dysfunction after two hours of polarizing or depolarizing cardioplegic arrest in a porcine model. *Perfusion.* 2019; 34 (1): 67–75. DOI: 10.1177/0267659118791357. PMID: 30058944.
24. *Nakai C., Zhang C., Kitahara H, Shults C., Waksman R., Molina E.J.* Outcomes of del Nido cardioplegia after surgical aortic valve replacement and coronary artery bypass grafting. *Gen Thorac Cardiovasc Surg.* 2023; 71 (9): 491–497. DOI: 10.1007/s11748-023-01914-x. PMID: 36843184.
25. *Abigail W., Aboughdir M., Mahbub S., Ahmed A., Harky A.* Myocardial protection in cardiac surgery: how limited are the options? A comprehensive literature review. *Perfusion.* 2021; 36 (4): 338–351. DOI: 10.1177/0267659120942656. PMID: 32736492.
26. *Zandstra T.E., Notenboom R.G.E., Wink J., Kiès P., Vliegen H.W., Egorova A.D., Schalij M.J., et al.* Asymmetry and heterogeneity: part and parcel in cardiac autonomic innervation and function. *Front Physiol.* 2021; 12: 665298. DOI: 10.3389/fphys.2021.665298. PMID: 34603069.
27. *Savchuk O.I., Skibo G.G.* Characteristics of nervous tissue after modeling of focal cerebral ischemia in rats at different periods of reperfusion. *Reports of Morphology.* 2018; 24 (3): 58–64. DOI: 10.31393/ morphology-journal-2018-24(3)-09.

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