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CARDIOPROTECTIVE EFFECTS OF PHARMOCOLOGICAL POSTCONDITIONING IN THE EXPERIMENTAL MODEL OF ISOLATED RAT HEART REPERFUSED AFTER COLD CRYSTALLOID CARDIOPLEGIA

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КАРДИОПРОТЕКТОРНЫЕ ЭФФЕКТЫ ФАРМАКОЛОГИЧЕСКОГО ПОСТКОНДИЦИОНИРОВАНИЯ В ЭКСПЕРИМЕНТАЛЬНОЙ МОДЕЛИ ИЗОЛИРОВАННОЙ РЕПЕРФУЗИИ СЕРДЦА КРЫСЫ ПОСЛЕ ХОЛОДОВОЙ КРИСТАЛЛОИДНОЙ КАРДИОПЛЕГИИ

Цель — оценить сократительную функцию и степень повреждения миокарда во время гипотермической ишемии и реперфузии в изолированных сердцах крыс, посткондиционированных левосименданом.

Материал и методы. Для оценки степени повреждения миокарда были определены показатели маркеров некроза миокарда, а именно СК МВ, ЛДГ. Для оценки сократительной функции миокарда определены коронарный кровоток, частота сердечных сокращений и давление в левом желудочке. Изучена динамика окислительно-восстановительных процессов при реперфузии, проведены гистологические исследования.

Результаты. Были подтверждены кардиопротекторные эффекты левосимендана при реперфузии изолированного сердца после кардиоплегической ишемии. Общие эффекты характеризуются уменьшением индуцированного реперфузией высвобождения маркеров повреждения миокарда, снижением тяжести патологических изменений миокарда и уменьшением интенсивности свободнорадикальных реакций в миокарде.

Вывод. Снижение тяжести повреждения кардиомиоцитов и восстановление сократительной функции миокарда с помощью кардиопротекторного действия левосимендана привело к сокращению интенсификации свободнорадикального окисления в модели изолированного сердца крысы.

Ключевые слова: изолированное сердце, кардиоплегическая ишемия, реперфузия, левосимендан, посткондиционирование.

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Aim: To assess contractile function and the degree of myocardial damage during hypothermic ischaemia and reperfusion in isolated rat hearts, postconditioned with levosimendan.

Material and methods. To estimate the extent of myocardial damage, the values of the markers for myocardial necrosis, namely CK MB, LDH, were measured. To assess the myocardial contractile function, coronary blood flow, heart rate, left ventricular pressure were evaluated. The dynamics of the redox processes during reperfusion have been studied. The histological study was performed.

Results. Cardioprotective effects of levosimendan in isolated heart reperfused after cardioplegic ischemia have been confirmed. The overall effect results in a reduction of reperfusion induced release of enzyme markers for myocardial damage, a reduction of the severity of myocardial pathological changes and a reduction of the intensity of free radical reactions in the myocardium.

Conclusion. Reduced severity of cardiomyocytes damage and restoration of myocardial contractile function using the cardioprotective drug levosimendan resulted in the reduction of intensification of free radical oxidation in isolated rat heart model.

Key words: isolated heart, cardioplegic ischemia, reperfusion, levosimendan, postconditioning.

Introduction

High prevalence of cardiovascular disease among the world standard population is associated with increased number of open-heart surgeries under cardiopulmonary bypass and the need to introduce heart transplant techniques into the clinical practice. However, there is no routine effective and generally accepted method of myocardial protection against ischemia-reperfusion injury. This fact results in the need to expand treatment options for cardioprotection and to study its underlying mechanisms. Recent studies have indicated that reperfusion conditions are critical for salvaging viable myocardium, following ischemic injury, and preventing necrosis, causing lethal reperfusion-induced injury. Therefore, therapeutic approaches for ischemic postconditioning against ischemia-reperfusion injury seem to be promising for myocardial protection [1]. Furthermore, the protective interventions during the early stages of reperfusion are much simpler from the practical point of view. A new calcium-sensitizing cardiotonic drug, levosimendan, may be regarded as a pharmacological postconditioning agent capable of activating cardioprotective responses in the myocardium [2; 3]. A number of experimental studies have demonstrated its cardioprotective effects [4–6], but the majority of these studies were conducted in the models with reperfusion subsequent to 1 hr of myocardial ischemia. However, the introduction of heart transplant techniques into the clinical practice is associated with prolonged cardioplegic ischemic arrest.

Thus, the efficacy of levosimendan postconditioning against myocardial ischemia-reperfusion injury in prolonged global cardioplegic ischemia requires further experimental studies. An isolated heart model seems to be convenient model to assess its effect.

Aim: To study the cardioprotective effects of levosimendan postconditioning in isolated rat hearts reperfused with cold crystalloid cardioplegia after 4 hrs of arrest.

Material and methods

Experimental protocol for isolated heart perfusion. The study was performed on isolated hearts of 60 Wistar rats (body weight (350±20) g). The animals were housed at a standard controlled temperature, fed a standard diet for small laboratory animals, and given water ad libitum in compliance with the requirements of the European Convention (Strasbourg, 1986). The study and its experimental protocol were approved and monitored by the Local Ethics Committee of the Research Institute. The study was conducted in the autumn-

winter period to eliminate the effect of seasonal variations in heart resistance to ischemia-reperfusion injury. After rats were anaesthetized with 45 mg/kg of ethaminal, the chest was opened. The heart was excised, the aorta was isolated and connective tissues were removed. The aorta was cannulated and the heart was retrograde perfused at a perfusion pressure of 80 cmH_2O according to Langerdoff model at 37 °C for 20 min with Krebs-Henseleit buffer of the following composition (mM): NaCl — 118.0; KCl — 4.7; $MgSO_4$ — 1.2; KH_2PO_4 — 1.2; $CaCl_2$ — 2.0; glucose — 5.5; $NaHCO_3$ — 25.0. The perfusion buffer was equilibrated with a gas mixture of 95 % O_2 and 5 % CO_2 to pH 7.4. The hearts were arrested infusing cold cardioplegic solution (4 °C, Custodiol) into the coronary blood flow at a constant flow rate (100 ml/hr, 20 gtts/ml) for 8 minutes delivered by an infusion pump (OT-701, Japan). Cardioplegic ischemia was simulated by placing the heart in a bath with cold (4 °C) cardioplegic solution (Custodiol, 20 ml) for 240 minutes. The temperature regime was chosen according to the available standards, requiring the use of cold crystalloid cardioplegic solutions with external cooling of the heart (the target temperature of the heart can not be exceeded +11 °C). Post-ischemic reperfusion was initiated according to Langendorff model with oxygenated Krebs-Henseleit buffer for 30 min.

Pharmacological postconditioning. In this study, the effects of cardiotonic agent levosimendan on ischemic myocardium were assessed. A stock solution was diluted to a concentration of 0.1 mmol/l using Krebs-Henseleit buffer. The dose of levosimendan sufficient to provide protective effects on ischemia-reperfusion injury in isolated rat heart was empirically chosen according to the literature-based evidence [9]. Levosimendan was infused over 8 min into the coronary artery at the onset of the reperfusion (levosimendan group). In the control group, the hearts were perfused according to the mentioned above protocol without pharmacological agent (custodiol group).

Assessment of biochemical markers of myocardial damage. Levels of organ-specific markers of myocardial damage, namely myocardial creatine kinase isoenzyme (CK-MB) and lactate dehydrogenase (LDH), were measured in perfusate effluent at 10 and 30 min of reperfusion. Activities of myocardial markers CK-MB and LDH were evaluated by enzyme kinetics and expressed in international units per liter (IU/L) with an automatic biochemical analyzer SAPPHIRE-400 (Russia) using commercial kits for LDH (Diakon-DS, Russia) and CK-MB (DiaSys Diagnostic Systems GmbH, Germany).

Evaluation of contractile function. Contractile parameters of isolated hearts were recorded in the isovolumetric regimen using a latex balloon catheter inserted into the left ventricular cavity connected to a pressure transducer and amplifier module with an MP36 System (Biopac Systems, Inc., California, USA). The balloon was filled with distilled water, the volume of balloon was sufficient for creating left ventricular end-diastolic pressure of 10 mm Hg. The intraventricular pressure curve was recorded to assess cardiac function. Further contractile parameter measurements of isolated hearts were performed using the software BSL PRO 3.7.3 (Biopac Systems, Inc., CA, USA). Physiological parameters of isolated hearts were monitored at all stage of reperfusion: heart rate (HR, bpm), left ventricular developed pressure (LVDevP, mm Hg) (obtained by subtracting the diastolic pressure from the systolic pressure), end-diastolic pressure (EDP, mm Hg) and systolic pressure (SP, mm Hg).

Assessment of coronary blood flow. Coronary blood flow (CBF) was determined by the amount of perfusate flowing through the coronary arteries per minute, ml/min. CBF was registered after 10 min of perfsion with Krebs-Henzelyayta before ischemia at baseline and at 10 and 30 min of reperfusion.

Histological study. Histological study of rat myocardium in the levosimendan and custodiol groups was performed using a light microscope AXIO Imager. A1 (CarlZeiss, Germany). The samples were processed and stained with hematoxylin and eosin according to the standard procedure. Digital images were obtained using the software AXIO Vision. The histological study of the samples was performed at 20x and 40x objective lens magnifications and 10x and 10x eyepiece lens.

Assessment of the extent of damaged zone. The extent of irreversible myocardial damage was assessed using the stained heart slices (SHS). The necrotic surface was measured as the infarct volume to the heart total volume and expressed as a percentage. After the reperfusion was completed, the coronary artery was ligated and 0.5 ml of a 5% Evans Blue was injected intravenously. After visualization of the border between perfused and ischemic tissues, the heart was quickly removed and cut into 5 to 6 uniform transverse slices of 2 mm thickness. Basal and apical surfaces of all sections were photographed using a C-400 (Olympus) digital camera mounted on a MBC-10 microscope (LOMO, St. Petersburg). Images of the studied samples were computer-processed with the further calculation of the area between two zones. Then, the total lesion volume was calculated over all slices (the volume of irreversibly damaged tissue/the total volume of tissues). The statistical significance of all differences of functional data for each timepoint as well as the infarct size were assessed using the nonparametric Mann-Whitney test. Data are presented as means and standard deviations.

Results and Discussion

The initial period of reperfusion in levosimendan and custodiol groups was accompanied by a significant increase in LDH and CK-MB activities, compared with baseline values. Activities of these markers showed a tendency to decrease during the reperfusion period in both groups (Fig. 1). At the end of reperfusion, in the levosimendan group, levels of enzyme markers activity returned toward preischemic levels, whereas in the custodiol group, they were significantly higher compared with baseline values in both groups. The dynamics of recovery of contractile function in isolated hearts during reperfusion in

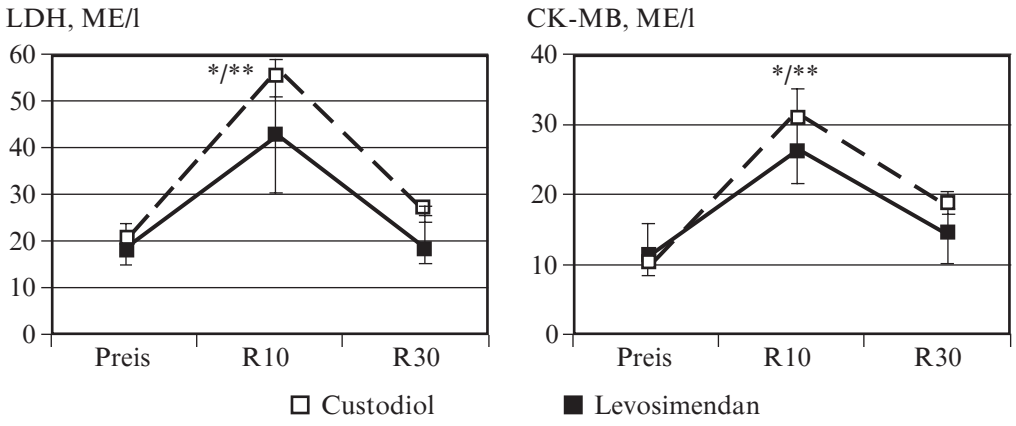


Fig. 1. Dynamics of LDH and CK-MB in the perfusate effluent from isolated rat hearts in the custodiol and levosimendan groups during different stages of reperfusion: On fig. 1, 2: Preis — preischemic values; R 10, R 30 — minutes of reperfusion; * — $p<0.05$ between the experimental groups; ** — $p<0.05$ according to preischemic values

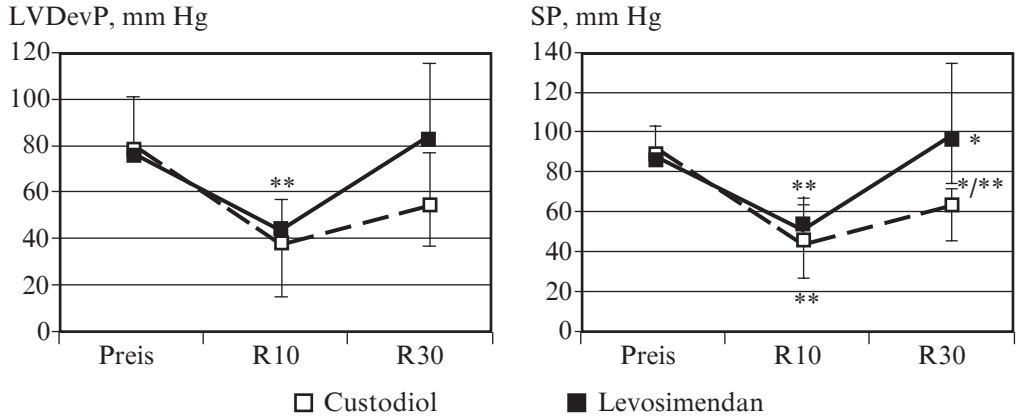


Fig. 2. Dynamics of recovery of left ventricle developed pressure and systolic pressure in the coustodiol and levosimendan groups during reperfusion

the levosimendan group and custodial group are shown in Fig. 2. After the first 15 min of reperfusion, LVDevP fell to values less than preischemic levels in both groups, indicating poor left ventricular contractile function. However, at this stage of reperfusion, LVDevP levels were significantly higher in the levosimendan group ($p < 0.0273$), than in the custodiol group. A similar trend was observed in ESP values, which did not return to baseline values ($p < 0.0175$) at this stage of reperfusion in both groups. Thus, after 15 min of reperfusion and complete restoration of coronary blood flow, the levosimendan and custodial groups demonstrated impairment of myocardial contractile function, indicating myocardial stunning, caused by a disturbance of cellular calcium homeostasis and free-radical damage. In this case, decreased myofilament calcium sensitivity resulted in poor contractile function of cardiomyocytes. By the end of the reperfusion period, contractile parameters recovered in the levosimendan group to preischemic values, whereas in the custodiol group they were significantly higher in comparison with baseline values, and those, obtained in the levosimendan group. During the reperfusion period, the dynamics of changes in heart rate and end-diastolic pressure in both groups was similar (Table 1). Coronary blood

Table 1

Myocardial contractile activity during reperfusion

Parameters		Groups, Me (25–75%)	
		custodiol	levosimendan
HR, bpm	Preis	204.0 (145.0–212.0)	
	R 15	103.0 (101.0–226.0)	151.0 (127.0–184.0)*, **
	R 30	101.0 (96.0–246.0)*	107.0 (103.0–150.0)*, **
EDP, mm Hg	Preis	5.1 (3.9–7.2)	
	R 15	9.5 (3.0–19.3)*	4.4 (4.1–8.0)*, **
	R 30	7.0 (5.9–14.6)*	13.0 (9.5–15.2)*

Note. Preis – preischemic values; R 15, R 30 – minutes of reperfusion; * — $p<0.05$ between the experimental groups; ** — $p<0.05$ according to preischemic values; HR — heart rate; EDP — end-diastolic pressure. Statistical significance — the non-parametric Mann–Whitney test.

flow recovered to preischemic values in both groups (Fig. 3). Thus, by the end of the reperfusion period, CBF was significantly higher in the custodiol group, compared with baseline values. According to the reperfusion dynamics, CBF decreased to preischemic values in the levosimendan group. This finding suggests that levosimendan does not exert vasodilator effects in 4 hrs of arrest after cardioplegia and reperfusion in isolated rat heart model. In this case, increased CBF in both groups at the initial reperfusion stage may be provoked by an adaptive mechanism that restores blood flow to unsupplied ischemic tissue. Taking into account that levosimendan administration attenuates reperfusion injury, the need to activate this mechanism gradually decreases. The main mechanism contributing to the protective effect of levosimendan is its ability to increase the calcium sensitivity of the contractile proteins without increased oxygen consumption. We suggest this mechanism to contribute to the recovery of contractile function in isolated rat hearts postconditioned with levosimendan after 4 hrs of cardioplegic ischemia, thus, eliminating myocardial stunning. In case of custodial-induced cardioprotection during the whole reperfusion period, persistent myocardial dysfunction may be associated with both cardiomyocyte ischemia-reperfusion injury (necrosis or apoptosis), and persistent myocardial dysfunction without necrosis (stunning). Despite significant differences in reperfusion release of enzyme marker for myocardial destruction between the studied groups, the histological analysis showed similar morphological changes and their expression in the studied samples. The following signs of myocardial ischemia-reperfusion injury were identified in the custodiol and levosimendan groups upon histological examination: regions of longitudinal fiber disarrangement, cross-fragmentation of muscle fibers, cardiomyocyte disarray and their uneven cytoplasmic staining. The cardiomyocyte nuclei were oval, some of them were extruded, unevenly stained (Fig. 4). There was no violation of the endothelial integrity of the samples of investigation. Importantly, the above-mentioned morphological changes in the myocardium tended to be less pronounced in the levosimendan group than in the custodiol group (Fig. 5). The size of ischemic region in the custodial group was 63.3 (59.4–70.3) % of the total myocardial surface area.

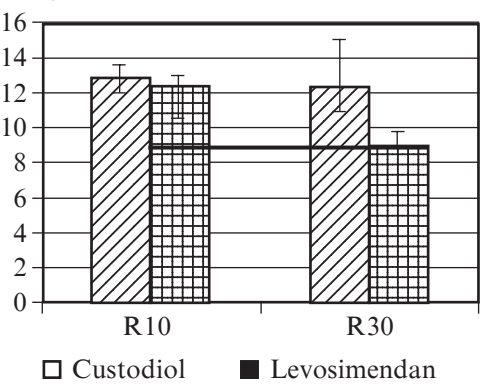


Fig. 3. Coronary blood flow during different reperfusion stages in the studied groups: * — p<0.05 between the experimental groups; ** — p<0.05 according to preischemic values; R 10, R 30 — minutes of reperfusion

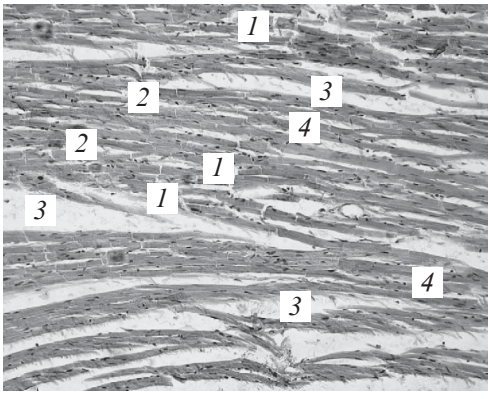
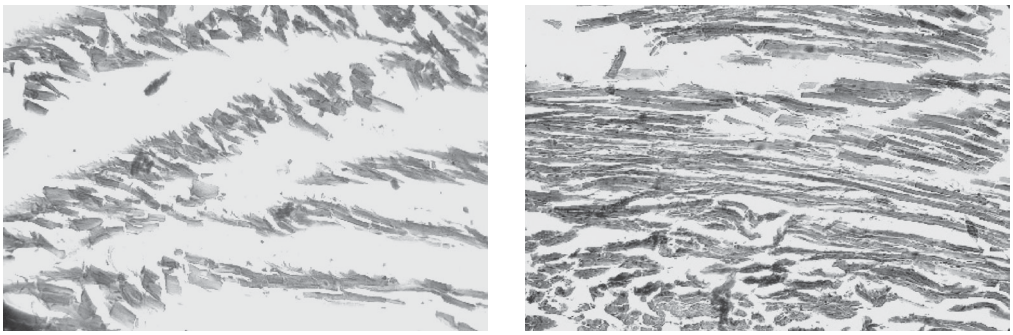


Fig. 4. Histological imaging of the myocardium in the studied groups. Cross-section. Hematoxylin-eosin staining (× 200): *1* — cross-fragmentation; *2* — uneven cytoplasmic staining; *3* — longitudinal fiber disarrangement; *4* — cardiomyocyte disarray



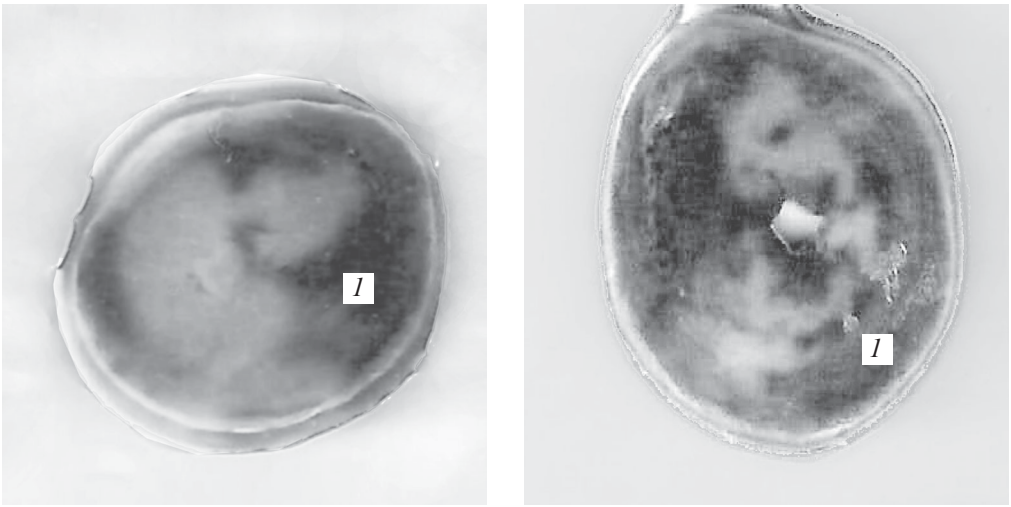
a *b*

Fig. 5. Morphological changes in the groups. Cross-section. Hematoxylin-eosin staining (× 200): *a* — custodiol group; *b* — levosimendan group

The levosimendan group demonstrated a statistically insignificant tendency to a decrease in the infarct size to 56.6 (55.2–62.0) % (Fig. 6). The absence of statistically significant infarct-limiting effect of levosimendan postconditioning suggests that ischemia injury prevails over reperfusion injury in the formation of myocardial necrosis

Conclusion

The obtained results indicated the cardioprotective effect of levosimendan postconditioning on myocardium after prolonged ischemia. It is represented with preserved cellular respiration and oxidative phosphorylation, associated with the reduction of myocardial reperfusion injury. Ultimately, this led to the restoration of the functional parameters of the heart muscle to baseline values. However, the analysis of the obtained results suggests that prolonged cardioplegic ischemia is associated with the formation of myocardial necrosis during the ischemic stage, resulting in the need to expand the options for cardioprotection, namely to use modified cardioplegic solution or to administer precon-



a *b*

Fig. 6. The volume of damaged region in the groups: *a* — the custodiol group; *b* — the levosimendan group: *1* — viable tissue with preserved enzymatic activity

ditioning with pharmacological agents. This approach may allow prolonging the relatively safe ischemic period, enhancing myocardial salvaging and reducing reperfusion injury.

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A 20-YEAR EXPERIENCE OF RHABDOMYOLYSIS TREATMENT, COMPLICATED BY ACUTE RENAL FAILURE

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ДВАДЦАТИЛЕТНИЙ ОПЫТ ЛЕЧЕНИЯ РАБДОМИОЛИЗА, ОСЛОЖНЕННОГО ОСТРОЙ ПОЧЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ

Цель — проанализировать эффективность неотложной помощи при рабдомиолизе с острой почечной недостаточностью.

Материалы и методы. В клиниках трех учреждений изучен двадцатилетний опыт интенсивной терапии по историям болезни 284 пациентов с синдромом позиционного сдавления и тромбозами магистральных сосудов, осложненным рабдомиолизом и сопровождавшимся острой почечной недостаточностью в олигурической и анурической стадиях. Проанализированы частота осложнений, количество и качество процедур экстракорпорального очищения крови, доступы, эффективность хирургических вмешательств, показатели летальности в десятилетнем интервале (1993–2002 и 2003–2012 гг.).