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OPTIMAL TEMPERATURE CONDITIONS FOR PROLONGED TRANSPORT OF DONOR HEARTS: AN EXPERIMENTAL STUDY

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Objective: to compare the effectiveness of extended heart preservation (up to 6 hours) at a temperature of +4 to +8 °C with the standard method. **Materials and methods.** The study was conducted using male Landrace pigs weighing 40–60 kg (n = 6). The experimental group (n = 3) underwent heart preservation at an optimized temperature of +4 to +8 °C for 6 hours prior to transplantation. In the control group (n = 3), hearts were preserved using the standard method for the same duration. Following preservation, coronary perfusion was restored *ex vivo*, cardiac activity was reinitiated, and myocardial function was evaluated alongside biochemical markers of cardiac tissue injury. **Results.** Following the resumption of blood supply and cardiac activity, both groups showed a reduction in superoxide dismutase (SOD) and malondialdehyde (MDA) levels. In the experimental group (preserved at +4–8 °C), SOD and MDA levels decreased from 12.31 to 8.85 ng/mL per 1 g of protein, while in the control group (standard method), levels declined from 12.04 to 9.23 ng/mL per 1 g of protein. In the experimental group, the level of heart-type fatty acid-binding protein (H-FABP) remained stable, whereas in the control group, it declined from 1.42 to 1.06 ng/mL per 1 g of protein. After prolonged preservation, receptor-interacting protein (RIP) kinase concentrations increased more markedly in the control group (from 0.071 to 0.086 ng/mL) than in the experimental group (from 0.024 to 0.028 ng/mL per 1 g of protein). Additionally, caspase-8 levels in the experimental group significantly decreased from 0.04 to 0.013 ng/mL per 1 g of protein. No significant differences were observed in von Willebrand factor levels between the two groups. However, histological analysis in the control group revealed muscle fiber fragmentation and widespread coagulopathy in myocardial tissue following standard cold ("ice") preservation. **Conclusion.** This pilot experimental study indicates that long-term preservation of donor hearts at a controlled temperature of +4–8 °C is both effective and safe when compared to the conventional preservation method.

Keywords: preservation, heart transplantation, coronary perfusion, graft dysfunction.

INTRODUCTION

Progressive heart failure (HF) is a life-threatening, disabling condition and one of the leading causes of mortality worldwide. For patients with end-stage HF, heart transplantation (HT) remains the only definitive treatment. However, the demand for donor hearts continues to rise, while the supply of deceased donors remains insufficient, resulting in increased waitlist mortality [1]. The solution to the problem of donor organ shortage has been a subject of debate among transplantologists for many years. With conventional cold storage – using a triple-bag system placed in an ice container – the optimal cold ischemia time is approximately 4 hours [2, 3], with an absolute maximum of 6 hours [4]. Prolonged ischemia increases the risk of ischemia-reperfusion injury (IRI), which can lead to irreversible damage, most notably primary graft dysfunction [5]. Transporting the organ in an ice-filled thermal container causes uncontrolled and uneven cooling. When the temperature falls to +2 °C, there is a risk of cold-induced injury to cardiomyocytes; at 0 °C, these changes may become irreversible [2].

The combined challenges of IRI and the persistent shortage of donor organs underscore the need to optimize organ transport technologies and to develop both perfusion and non-perfusion preservation methods. The Paragonix SherpaPak® Cardiac Transport System (Paragonix Technologies, Cambridge, MA) is a portable device designed to maintain the heart graft at an optimal temperature regardless of external conditions, thereby eliminating the risk of cold-induced myocardial injury and reducing the likelihood of primary graft dysfunction. The system preserves the organ within a controlled temperature range of +4 to +8 °C for up to 24 hours, ensuring uniform cooling, reducing metabolic demands, and protecting against IRI. While clinical data exist for its use in short-duration transport (<4 hours), its effectiveness under conditions of prolonged ischemia remains unproven. Moreover, the high cost (~$20,000) and lack

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of regulatory certification currently make it impossible to use the system in Russia [6, 7].

Published positive results on the use of the SherpaPak system for donor heart preservation of up to 4 hours, combined with the significant shortage of available heart transplants due to the underutilization of many donor centers, highlight the need to investigate longer preservation times under controlled cold ischemia. Extending safe preservation duration could expand the geographical reach of donor programs while reducing an IRI risk.

Objective of the study: To experimentally evaluate the feasibility of extended heart preservation for 6 hours at a controlled temperature of +4 to +8 °C compared with standard ice storage for the same duration.

MATERIALS AND METHODS

The study was conducted in compliance with the Rules for the Care and Use of Laboratory Animals. The experimental subjects were large laboratory animals – male mini-pigs weighing 40–60 kg (n = 6). Animals were randomly assigned to two groups: a control group (n = 3), in which hearts were preserved using the standard cold storage method, and an experimental group (n = 3), in which hearts were preserved under controlled cold ischemia conditions.

Animal housing, care, experimental procedures, observation, and euthanasia were carried out in accordance with the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, March 18, 1986). Ethical approval for the study was obtained from the Bioethics Committee of Meshalkin National Medical Research Center (Minutes of the meeting dated June 8, 2023, No. 2, agenda item No. 1). During the experiments, continuous monitoring included invasive arterial pressure via catheterization of the left carotid artery, central venous pressure via catheterization of the left jugular vein, heart rhythm by electrocardiography, body temperature, blood gas composition, activated clotting time, and cardiac hemodynamics using transesophageal echocardiography and Swan–Ganz catheterization. Vital parameters were recorded with an IntelliVue MP70 monitor (Philips, Germany).

Following surgical access via median sternotomy and isolation of the major vessels, all required diagnostic procedures were performed in accordance with the study protocol, including echocardiography as well as collection of laboratory and morphological samples. After occlusion of the aorta as close as possible to the origin of the brachiocephalic trunk, 3 liters of Bretschneider cardioplegic solution (4 °C) were administered into the aortic root. The heart was then explanted and packaged using the standard triple-bag method. In the experimental group, the graft was placed in a medical refrigerator with continuous temperature monitoring at +4 to +8 °C; in the control group, it was placed in a transport container with ice and coolants. Both preservation methods were maintained for 6 hours.

After the preservation period, perfusion of the heart with oxygenated blood was initiated using a heart–lung machine, starting at an aortic pressure of 40–50 mmHg and gradually increasing to approximately 70 mmHg within 15 minutes. Upon restoration of coordinated myocardial contractions, tissue biopsies and diagnostic tests were performed for comparative analysis.

To assess left ventricular function by ultrasound, cardiac activity was restored under constant volume conditions using an autoperfused complex model (Fig. 1). In this setup, blood was pumped by the heart's own contractions through an oxygenator into a reservoir, from

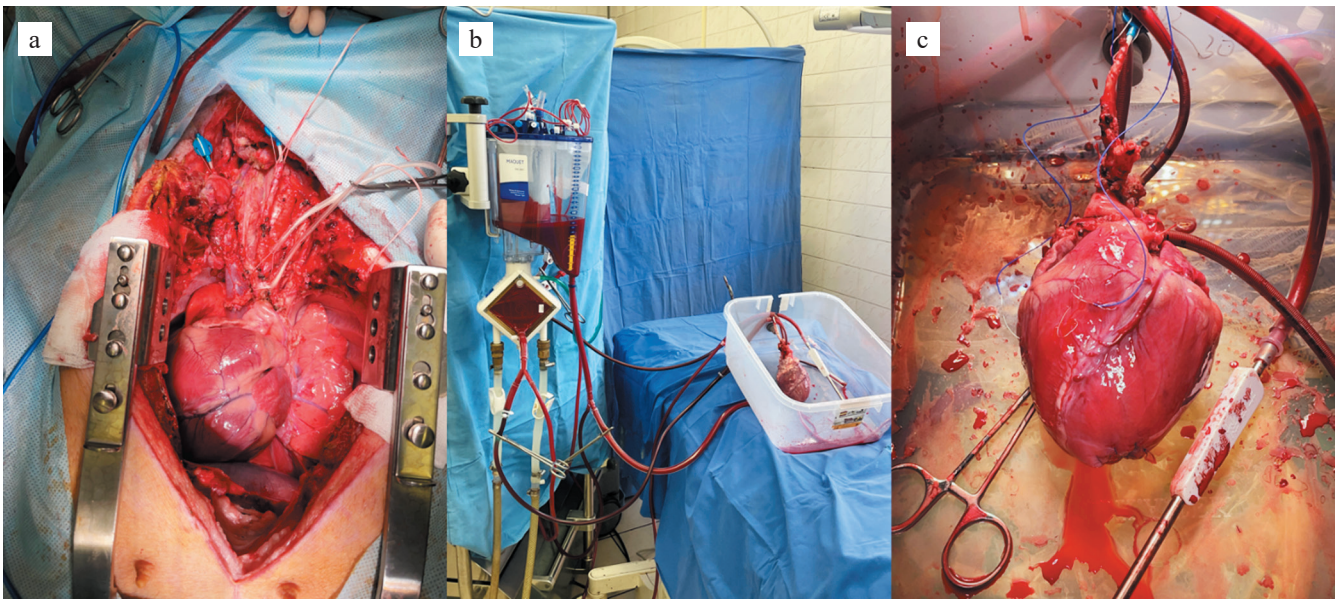

Fig. 1. Heart appearance: a, b – before preservation; c – after reperfusion

Fig. 2. Echocardiographic assessment of the heart during *ex vivo* perfusion

which it returned by gravity to the left atrium and right heart chambers. Perfusion and monitoring of the heart were performed for 1 hour after restoration of cardiac activity.

Echocardiography was performed using a portable multifunctional ultrasound system, the Philips CX50 (Philips Ultrasound, USA), with ECG synchronization and a sector phased-array transducer (S5-1). The transducer was placed *ex vivo* along the long axis of the left ventricle and in the apical four-chamber position, using a water-filled glove to enlarge the imaging window (Fig. 2). Cardiac function was assessed by determining the left ventricular ejection fraction (LVEF) and cardiac output (CO). The LVEF was calculated using Simpson's method in the apical four-chamber view according to the formula: LVEF (%) = (EDV – ESV) / EDV, where EDV is the left ventricular end-diastolic volume (mL), and ESV is the end-systolic volume (mL). Cardiac output was calculated using the formula: CO (L/min) = (π × (LVOTD/2)^2 × VTI × HR)/1000, where LVOTD is the Left Ventricular Outflow Tract Diameter (cm), VTI is the velocity time integral (cm), and HR is the heart rate (beats per minute).

During the experiment, a protocol was drawn up in accordance with which myocardial tissue samples were collected to determine the levels of caspase-8, RIP kinases, nitric oxide (NO), prostacyclin, prostaglandin H2, and von Willebrand factor. Blood samples were also obtained from the central vein to measure superoxide dismutase and heart-type fatty acid-binding protein (FABP-H) as biomarkers of oxidative stress. Sampling was conducted both before organ removal and after reperfusion of the heart in both study groups.

The objectives of the comparative study of myocardial morphology and tissue homeostasis after preservation at target temperature parameters (+4 to +8 °C) versus standard ice preservation for 6 hours – using atomic force microscopy and electron microscopy – were as follows:

1) To conduct an *in vitro* analysis of cardiomyocyte cell death (apoptosis and necrosis) after heart preservation at target temperature parameters (+4 to +8 °C) versus standard ice preservation for 6 hours, based on quantification of caspase-8 and RIP kinase levels in myocardial tissue extracts using enzyme-linked immunosorbent assay (ELISA) kits from specialized manufacturers.
2) To determine the extent of myocardial injury after preservation at +4 to +8 °C and standard ice preservation for 6 hours by measuring levels of cardiac FABP-H, troponin I, malondialdehyde, and superoxide dismutase in tissue extracts using ELISA-based kits.
3) To compare the preservation of total endothelial regulatory function under both temperature conditions by measuring stable NO, prostacyclin, prostaglandin H_2, and von Willebrand factor using ELISA kits from specialized manufacturers.

RESULTS

Data on the functional state of the myocardium were obtained through echocardiographic assessment following preservation at the specified temperature (+4–8 °C) and after standard ice preservation. Given the variability of cardiac functional and hemodynamic parameters among laboratory animals in both groups, direct comparison between the groups was not feasible. Nevertheless, it can be noted that within each individual group, after reperfusion and restoration of cardiac activity, myocardial function and hemodynamic parameters returned to baseline values and remained stable throughout the observation period (1 hour). A detailed comparative analysis of myocardial morphology after 6 hours of preservation at target temperatures (+4–8 °C) and standard ice preservation was also conducted.

Morphological changes in the myocardium in the study group (target temperature) were predominantly reversible and were characterized by Grade I–II contracture-type damage to the contractile apparatus, intracellular and interstitial edema, and mild coagulopathy. By contrast, in the standard cold ("ice") preservation group, a number of changes were largely irreversible,

with damage primarily of a lysosomal type, accompanied by fragmentation of muscle fibers and pronounced widespread coagulopathy in the muscle tissue (Figs. 3 and 4).

Immunoenzymatic assessment of ischemic myocardial injury included assessment of superoxide dismutase (SOD) and malondialdehyde (MDA) levels, which serve as markers of oxidative stress during and after ischemia. Interestingly, the results were paradoxical. After prolonged preservation, followed by reperfusion and restoration of cardiac activity, both groups demonstrated a decrease in SOD and MDA levels: from 12.31 to 8.85 ng/ml per 1 g of protein in the study group (+4–8 °C), and from 12.04 to 9.23 ng/ml per 1 g of protein in the control group (Figs. 5 and 6). A similar trend was noted for heart-type fatty acid-binding protein (H-FABP), which is localized in the cytoplasm of cardiomyocytes and is released rapidly into the systemic circulation in response to cellular damage due to its small molecular size and cytoplasmic localization. In the study group, H-FABP level remained unchanged, whereas in the control group it decreased from 1.42 to 1.06 ng/ml per 1 g of protein (Fig. 5).

An assessment of cell death mechanisms was also performed, with particular attention to regulated necrosis (necroptosis). Upon activation of necroptosis receptors, such as Toll-like receptors 3 and 4, autophosphorylation and activation of RIPK1 and RIPK3 occurs. Analysis of RIP kinase levels after prolonged preservation revealed a more pronounced increase in enzyme concentration in the control group compared with the study group – from 0.071 to 0.086 ng/mL per 1 g of protein in the control

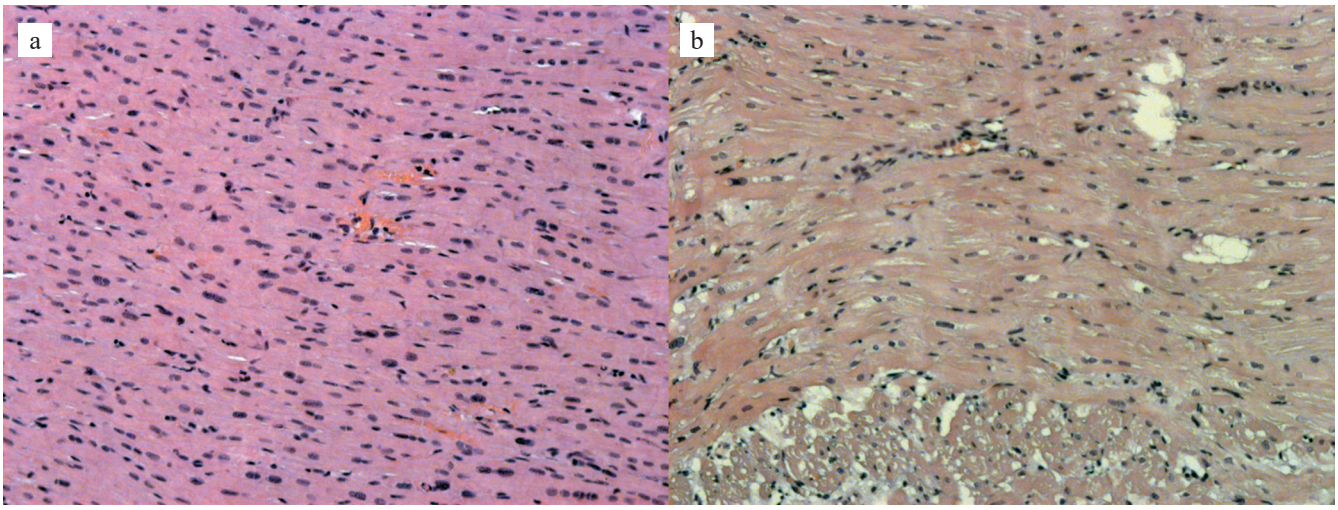

Fig. 3. Microscopic examination of the myocardium (Sample No. 1): a – control group: myocardial fibers are uniform in diameter and largely intact; moderate interstitial edema is observed in some areas, with isolated mononuclear cells present; b – experimental group: areas of perinuclear edema and signs of myofibril lysis are evident. Hematoxylin and eosin stain; 200× magnification

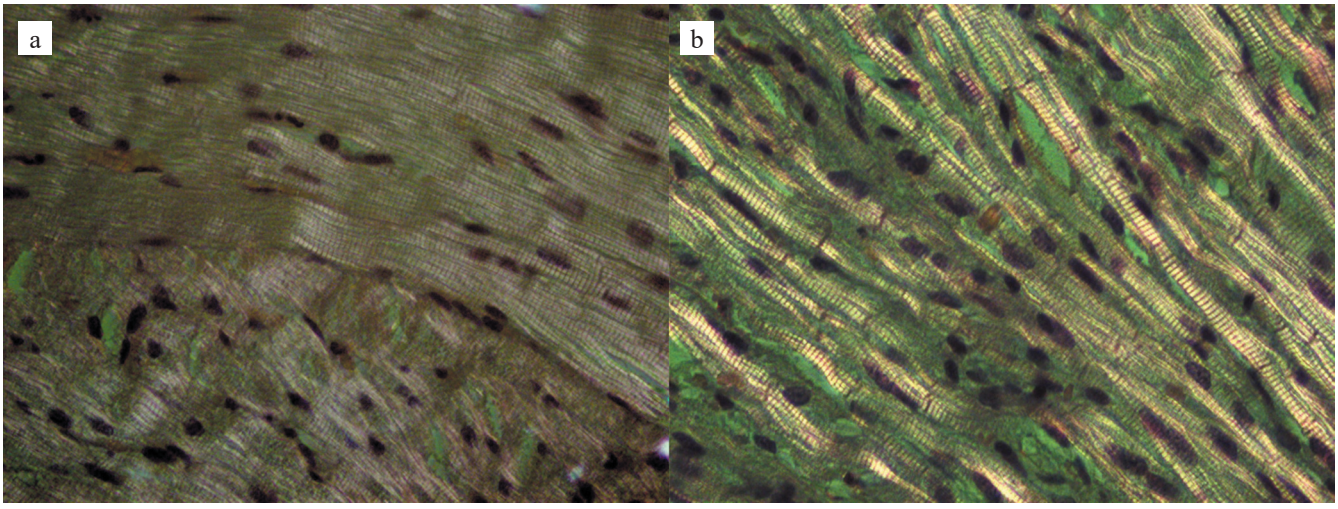

Fig. 4. Microscopic examination of myocardium (Sample No. 2): a – control group: preserved transverse striations of cardiomyocytes; areas of mild to moderate contracture are noted; b – experimental group: focal myofibril lysis with loss of transverse striations in cardiomyocytes. 630× magnification

group, and from 0.024 to 0.028 ng/mL in the study group (Fig. 6).

Apoptosis is a regulated form of cell death triggered by internal or external stimuli. Unlike necroptosis, where RIPK1, RIPK3, and MLKL play a central role, apoptosis is caspase-dependent and characterized by a decrease in cell volume, chromatin condensation (karyopyknosis), and subsequent chromatin fragmentation (karyorrhexis). Analysis of caspase-8 (Casp8) level in the study group revealed a decrease from 0.04 to 0.013 ng/ml per 1 g of protein (Fig. 7).

When von Willebrand factor was analyzed, no distinct changes were observed in either group after prolonged preservation. In the study group, levels were 4.17 and 3.99 ng/ml, and in the control group 7.07 and 6.84 ng/ml, respectively (Fig. 7), despite its initially higher baseline concentration in the control group.

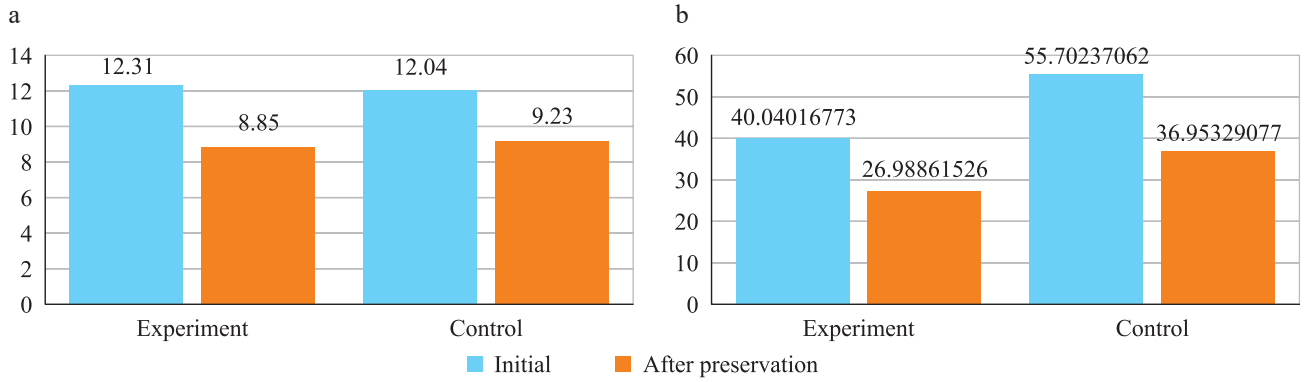

Fig. 5. Biochemical dynamics following reperfusion: a – changes in superoxide dismutase levels; b – changes in malondialdehyde levels

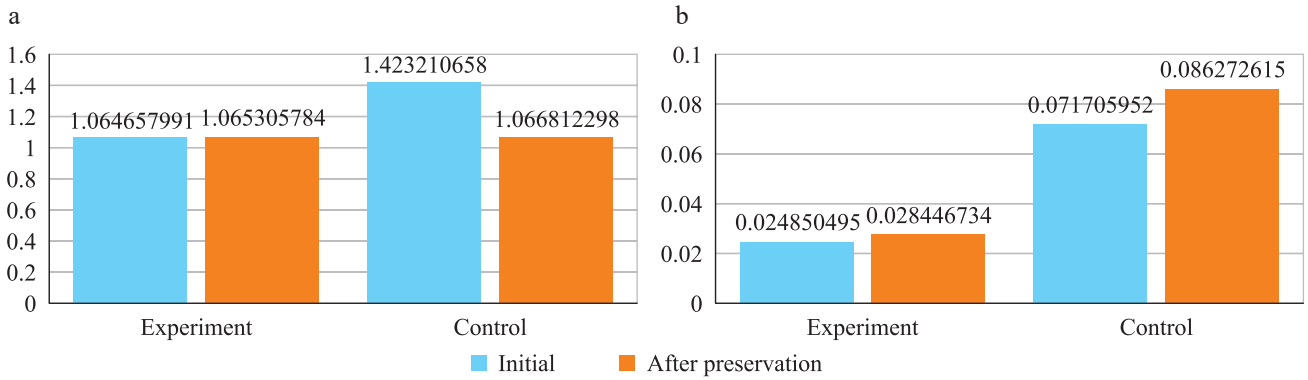

Fig. 6. Biochemical dynamics following reperfusion: a – changes in H-FABP levels; b – changes in RIP kinase levels, an indicator of necrosis

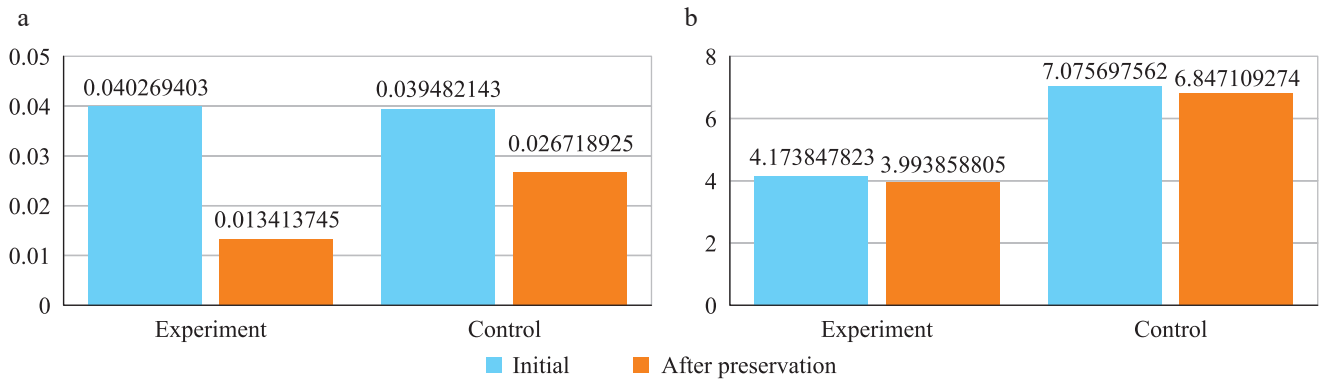

Fig. 7. Biochemical dynamics following reperfusion: a – changes in caspase 8 levels, an indicator of apoptosis; b – changes in von Willebrand factor levels, reflecting endothelial function

DISCUSSION

The optimal method for preserving heart transplants remains a cornerstone in addressing the problem of donor organ shortage. For decades, the standard method has involved classical static preservation of the graft in a thermal container filled with ice. However, this approach has begun to evolve due to the expansion of donor selection criteria and the development of both perfusion and non-perfusion preservation technologies, such as the Transmedics Organ Care System [8–10] and the Paragonix SherpaPak Cardiac Transport System. In this context, the development of a domestic method for static cold preservation of the heart – with controlled and uniform cooling – remains highly relevant for the Russian Federation, given the considerable geographical distances involved.

According to Van't Hoff's rule, a decrease in temperature by 10 °C reduces enzymatic activity by 1.5–2 times; however, the activity of the sodium–potassium pump also declines, leading to cellular edema during prolonged hypothermia [11]. Cold ischemia promotes anaerobic glycolysis and glycogenolysis, resulting in lactic acidosis. During reperfusion, reactive oxygen species are generated, contributing to irreversible cellular injury [12, 13]. Although high-energy phosphates may be preserved at donor organ temperatures between 0–4 °C, the risk of irreversible cold damage increases substantially, especially in the presence of uneven cooling of the graft [14, 15].

The ischemic heart is characterized by a state of oxidative stress, during which free oxygen radicals are released [16]. MDA serves as a key marker of lipid peroxidation and is produced as a result of the action of free radicals on polyunsaturated fatty acids [17]. An increase in MDA typically signifies damage to cardiomyocytes [18]. However, in our study, we observed a paradoxical decrease in MDA levels in both groups, as well as a concurrent reduction in SOD. SOD protects cells against oxidative stress by converting superoxide radicals into hydrogen peroxide, which is further degraded into water and oxygen by enzymes. It is noteworthy that under conditions of intense oxidative stress, the content of SOD itself may decrease [19]. Thus, SOD content plays a key role in regulating superoxide levels in tissues. As reported by Gheddouchi S. et al., SOD levels were significantly lower in patients with acute coronary syndrome, i.e., in conditions characterized by extremely high oxidative stress and myocardial ischemia.

A similar pattern was observed when analyzing the level of H-FABP, a cardiac fatty acid–binding protein that is essential for fatty acid metabolism in cardiomyocytes. Elevation of this biomarker generally reflects myocardial injury [20]. In this context, the absence of any change in H-FABP levels in the experimental group, along with a decrease in the control group, remains an open question and may warrant further investigation.

Another important indicator of acute myocardial injury is the family of RIP kinases (RIPK1 and RIPK3). These intracellular signaling proteins initiate necrotic pathways that result in rapid loss of plasma membrane integrity and release of pro-inflammatory cytokines [21, 22]. In our study, a more pronounced increase in RIP kinase levels was observed in the control group compared with the experimental group. Regarding von Willebrand factor, levels were initially elevated in both groups, and no statistically significant differences were detected after preservation. Since von Willebrand factor is stored in large amounts within Weibel–Palade bodies of endothelial cells, an increase in its concentration would typically indicate the onset of endothelial dysfunction [23].

Long-term preservation under controlled, uniform cold ischemia has the potential to extend the current 4-hour limit of graft viability by minimizing ischemia–reperfusion injury. This, in turn, could significantly expand the geographic reach of donor organ procurement and help alleviate the shortage of donor hearts.

CONCLUSION

Preservation under controlled hypothermia (+4 to +8 °C) demonstrates clear advantages over standard ice preservation, as evidenced by improved morphological findings and reduced activation of necroptotic pathways (RIP kinase), while showing no significant differences in contractile function, hemodynamic parameters, or biochemical markers of myocardial damage.

LIMITATIONS

The main limitations of this study include the small sample size of experimental animals, heterogeneity of baseline parameters, and the absence of a clear reference standard. In addition, the evaluation was based largely on changes in indicators relative to baseline values.

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The authors declare no conflict of interest.

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