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Normothermic Extracorporeal Perfusion as a Method of Donor Heart Conditioning in Experiment

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ABSTRACT

INTRODUCTION: Extracorporeal perfusion of transplants is a promising area that is actively studied to eliminate the existing shortage of donor organs. However, the optimal parameters and duration of extracorporeal perfusion that would not lead to impairment of the morphofunctional condition of transplants, have not been sufficiently studied.

AIM: To present the results of development and experimental testing of an original device for perfusion preservation of an isolated heart on the biomodel.

MATERIALS AND METHODS: An original perfusion device for preserving donor hearts has been developed and experimentally tested on mature outbred male rats. During 15-hour normothermic extracorporeal perfusion of the heart in the proposed device, its rhythmic and contractile function, temperature, pH of the perfusate, pressure in the aorta, hematocrit, pO_2 and pCO_2 in the perfusate were studied, the content of glucose, lactate, and creatine phosphokinase (CPK) activity in perfusate samples were determined.

RESULTS: During perfusion of isolated hearts, sinus rhythm was observed at a sufficient rate. Perfusate pH stayed within 7.3–7.4. Hearts were perfused at constant pressure in the aorta of 70 mm Hg in normothermic conditions (t=37°C). After stabilization of the heart function, the systolic pressure in the left ventricle was 96.0 [93.7; 98.5] mm Hg and remained without significant changes during 12 hours of perfusion; at 15 hours of perfusion, the parameter decreased by 15.0% to 82.0 [79.5; 84.2] mm Hg, p=0.01208. After stabilization of the heart function, diastolic pressure in the left ventricle was 4.0 [3.0; 5.0] mm Hg and remained without significant changes during 12 hours of perfusion; by 15 hours of perfusion, it increased 1.5 times to 6.0 [5.0; 7.0] mm Hg, p=0.0164. During the experiment, biochemical markers in the perfusate after 30 min of perfusion and stabilization were at the level of physiological values without significant dynamics within 12 hours of perfusion: glucose consumption was 80.5 [70.2; 85.5] μmol/(kg×min×mm Hg); lactate excretion — 35.7 [32.5; 44.2] μmol/(kg×min×mm Hg); CPK leakage — 95.8 [93.7; 111.3] IU/l. After 15 hours of perfusion, the level of glucose consumption by isolated hearts per unit of performed function increased significantly to 136.8 [130.5; 145.7] μmol/(kg×min×mm Hg), p=0.01208; lactate excretion and CPK leakage into the perfusate increased to 58.2 [55.7; 67.4] μmol/(kg×min×mm Hg), p=0.02144, and 229.7 [215.8; 242.4] IU/L respectively, p=0.01208.

CONCLUSION: The study showed that extracorporeal perfusion of the heart in the developed device allows maintaining its viability for 12 hours in conditions maximally close to physiological ones, and also conducting dynamic assessment of the functional and metabolic state of the organ.

Keywords: extracorporeal perfusion; conditioning; donor heart; device.

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Нормотермическая экстракорпоральная перфузия как метод кондиционирования донорского сердца в эксперименте

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АННОТАЦИЯ

Введение. Для устранения существующего дефицита донорских органов в качестве одного из перспективных направлений активно изучается экстракорпоральная перфузия трансплантатов. Однако оптимальные параметры и продолжительность экстракорпоральной перфузии, которые бы не приводили к ухудшению морфофункционального состояния трансплантатов, изучены недостаточно.

Цель. Представить результаты разработки и экспериментальной апробации оригинального устройства для перфузионной консервации изолированного сердца на биомодели.

Материалы и методы. Разработано и апробировано в эксперименте на половозрелых беспородных крысах-самцах оригинальное перфузионное устройство для консервации донорского сердца. В ходе 15-часовой нормотермической экстракорпоральной перфузии сердца в предлагаемом устройстве исследовали его ритмическую и сократительную функцию, температуру, pH перфузата и давление в аорте, гематокрит, pO_2 и pCO_2 в перфузате, определяли в пробах перфузата содержание глюкозы, лактата, активность креатинфосфокиназы (КФК).

Результаты. В ходе перфузии изолированных сердец отмечался синусовый ритм с достаточной частотой. Уровень pH перфузата оставался в пределах 7,3–7,4. Перфузия сердец проводилась при постоянном давлении 70 мм рт. ст. в аорте в условиях нормотермии (t=37°C). После стабилизации функции сердца систолическое давление в левом желудочке составило 96,0 [93,7; 98,5] мм рт. ст. и оставалось без значимых изменений в течение 12 часов перфузии, через 15 часов перфузии наблюдалось снижение данного показателя на 15% до 82,0 [79,5; 84,2] мм рт. ст., *p*=0,01208. После стабилизации функции сердца диастолическое давление в левом желудочке составило 4,0 [3,0; 5,0] мм рт. ст. и оставалось без значимых изменений в течение 12 часов перфузии; к 15 часам перфузии отмечалось повышение данного показателя в 1,5 раза до 6,0 [5,0; 7,0] мм рт. ст., *p*=0,0164. В ходе эксперимента биохимические маркеры в перфузате через 30 мин перфузии и стабилизации определялись на уровне физиологических значений без значимой динамики в течение 12 часов перфузии: потребление глюкозы составило 80,5 [70,2; 85,5] мкмоль/(кг × мин × мм рт. ст.); выделение лактата — 35,7 [32,5; 44,2] мкмоль/(кг×мин×мм рт. ст.); утечка КФК — 95,8 [93,7; 111,3] МЕ/л. Через 15 часов перфузии уровень потребления глюкозы изолированными сердцами на единицу выполняемой функции значительно повышался — до 136,8 [130,5; 145,7] мкмоль/(кг×мин×мм рт. ст.), *p*=0,01208; выделение лактата и утечка КФК в перфузат возрастали до 58,2 [55,7; 67,4] мкмоль/(кг×мин×мм рт. ст.), *p*=0,02144 и 229,7 [215,8; 242,4] МЕ/л соответственно, *p*=0,01208.

Заключение. В исследовании было показано, что экстракорпоральная перфузия сердца в разработанном устройстве позволяет поддерживать его жизнеспособность в течение 12 часов в условиях, максимально приближенных к физиологическим, а также проводить динамическую оценку функционально-метаболического состояния органа.

Ключевые слова: экстракорпоральная перфузия; кондиционирование; донорское сердце; устройство.

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INTRODUCTION

According to epidemiological studies, heart failure remains one main cause of morbidity and mortality of population in developed countries [1]. Despite the advancement of pharmacology, the only method of radical treatment of patients with end-stage heart failure is donor heart transplantation, which provides 10-year survival in up to 69.0% of patients [2, 3].

It is known that limited availability of transplantation care is in many aspects associated with the shortage of donor organs of the adequate quality optimally acceptable for recipients. One of promising directions proposed to enlarge the donor pool is the use of *extracorporeal machine perfusion* of organs with the aim both to prolong the transplant preservation time proper (anti-ischemic protection), and to 'rehabilitate' the consequences of ischemic and subsequent reperfusion injury to donor organs, and to select suitable transplants retrieved from donors with expanded assessment criteria and donors with irreversible circulatory arrest [4–7].

To date, the only system in the world for extracorporeal perfusion of donor hearts approved for clinical use is the Transmedics Organ Care System (Transmedics, USA). In this system, a combination of donor blood and an original solution is used as a perfusate for the heart; perfusion of the donor organ is carried out in a moderate hypothermia mode (34°C) [8, 9]. Apart from the extremely high cost, the main disadvantage of this device is the *inability to assess the parameters of cardiac contractility in real time*, which deserves attention, since these parameters, as previously shown in the PROCEED II study, are independent predictors of clinical outcomes of heart transplantation [10]. It should be noted that in the Russian Federation, there are patented developments and clinical experience in the use of machine perfusion to maintain the viability of donor kidneys and liver [4, 11, 12], but to date there is no information of the development of experimental and clinical devices for *prolonged extracorporeal perfusion of the donor heart* that would take into account high sensitivity of the myocardium to the situation of acute ischemia and the absence of significant reserves of high-energy substrates in the myocardium.

It should also be noted that the optimal physicochemical parameters (temperature and composition of the solution, duration, speed and pressure of perfusion) for realization of the cardioprotective effect of extracorporeal perfusion on the morphofunctional condition and energy potential of donor hearts, are not sufficiently investigated, which, in particular, may be due to complexity of methodological approaches to long-term anti-ischemic protection of the myocardium. The listed medical and biological aspects of extracorporeal heart perfusion require further acquisition and accumulation of scientific data.

The **aim** of this study to present the results of the development and experimental testing of an original device for perfusion preservation of an isolated heart on a translational biomodel.

MATERIALS AND METHODS

The experimental study was performed from December 2021 to September 2022 and approved by the Ethics Committee of Omsk State Medical University (Protocol No. 12 of November 24, 2021).

Description and operating principle of the perfusion device. The development of a perfusion device for preserving a donor heart is based on the experience of experimental studies on the Langendorff model of an isolated mammalian heart perfusion. As a prototype, an isolated heart perfusion setup based on the AD Instruments (Australia) system was chosen [13].

However, the design of the setup chosen as a prototype does not allow for prolonged perfusion of donor heart for the following reasons:

1) limited delivery of oxygen to the myocardium due to absence of an oxygenator, which leads to gradual suppression of the heart function already within an hour of perfusion;

2) use of Krebs–Henseleit crystalloid solution as perfusate leads to edema and dysfunction of the myocardium in a prolonged perfusion;

3) the known setup does not contain a pacemaker and defibrillator to correct possible disturbances in the rhythm of the donor heart during reperfusion;

4) in the known setup, the removal of tissue metabolism products from perfusate is not provided.

To ensure long-term normothermic perfusion of the donor heart, *a peristaltic pump, a left atrium cannula, an absorption filter, a membrane oxygenator, a pacemaker, etc. were additionally introduced* into the Langendorff cardiac perfusion setup [14].

An isolated heart is placed in the thermostatically controlled chamber. To record invasion pressure, a latex balloon is inserted in the left ventricle. Bioelectric activity of the heart is controlled in the 'on-demand' mode using a pacemaker/defibrillator with electrodes connected to a portable monitor. Solid arrows schematically indicate the movement of the perfusate in retrograde perfusion, and dashed arrows – in biventricular perfusion of the heart (Figure 1).

For retrograde heart perfusion, the aorta is cannulated. The cannula is connected to a perfusion column. Perfusion parameters are controlled using a pressure sensor and a flowmeter. Perfusate, having passed through the coronary system, is collected in a return reservoir. From

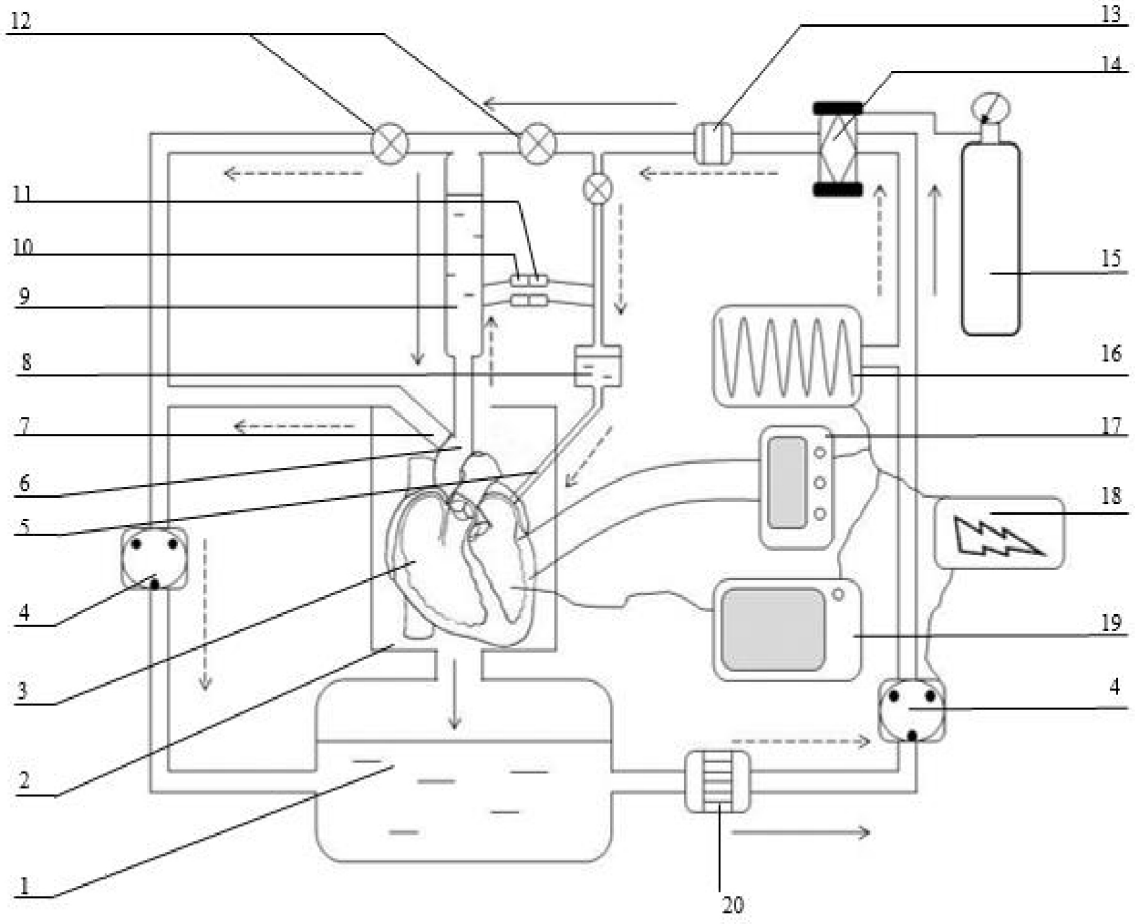

Fig. 1. A schematic diagram of setup for preservation perfusion and reconditioning of a donor heart: 1 — return reservoir, 2 — thermostatically controlled chamber, 3 — heart, 4 — peristaltic pump (2 pcs.), 5 — left atrium cannula, 6 — aortic cannula, 7 — pulmonary artery cannula, 8 — left atrial reservoir, 9 — perfusion column, 10 — perfusate pressure sensor (2 pcs.), 11 — flowmeter (2 pcs.), 12 — three-way valve (3 pcs.), 13 — air trap, 14 — oxygenator, 15 — gas cylinder, 16 — circulation thermostat with heater and cooler of perfusate, 17 — pacemaker/defibrillator, 18 — autonomous power supply, 19 — portable monitor, 20 — absorption filter.

there, using a peristaltic pump, perfusate flows through an absorption filter, an oxygenator connected to a gas cylinder, and an air trap.

For biventricular perfusion, the aorta, left atrium, and pulmonary artery are cannulated and the inferior vena cava is ligated. A latex balloon is inserted into the right ventricle through the superior vena cava to record invasive pressure. Perfusate from the left atrium reservoir flows through the left heart chambers and the aorta into the perfusion column. Having passed through the coronary bed, perfusate flows to the right heart chambers, then to the pulmonary artery, mixes with the perfusate from the aorta and is fed into the return reservoir by a peristaltic pump. From the reservoir, using a peristaltic pump, the perfusate flows through an absorption filter, an oxygenator connected to a gas cylinder, an air trap and flows into the left atrium reservoir.

Experimental protocol. For experimental testing of the operation of perfusion apparatus, sexually mature outbred male rats weighing 250–300 g were chosen as a biomodel. Experiments were conducted on 16 intact animals in compliance with the requirements of the European Convention on the Maintenance, Feeding,

and Care of Experimental Animals, as well as their Withdrawal from the Experiment and Subsequent Disposal (Strasbourg, 1986). The minimum sufficient number of experimental animals in a group, necessary to obtain reliable results, was calculated using the formula of F. Lopez–Jimenez et al. [15] and amounted to 8 animals.

After treatment of the surgical field, under face-mask anesthesia with diethyl ether, bilateral thoracotomy was conducted, major vessels were transected, the heart was retrieved and placed in Krebs–Henseleit solution cooled to +2°C–4°C. The composition of Krebs–Henseleit solution was as follows (in mmol/l): NaCl — 120; KCl — 4.8; MgSO4 — 2.5; $CaCl_2$ — 2.5; KH_2PO_4 — 1.2; $NaHCO_3$ — 25.0; Glucose — 5.5. After cannulation of the aorta, through the auricle of the left atrium, a latex balloon of constant volume connected to a portable monitor, was placed in the left ventricle and fixed with ligature. Under sterile conditions, the isolated heart was placed in the thermally controlled chamber of the setup, retrograde perfusion of the hearts was performed with Krebs–Henseleit solution through the aorta according to Langendorff; to the solution, autologous blood was added in the proportion 1:1, and 100 U/kg unfractionated heparin was administered every 4 hours, the perfusate was saturated with carbogen (95% O_2 + 5% CO_2), perfusion was performed at pressure 70 mm Hg and temperature 37°C. The restoration of cardiac activity, heart rate (HR), temperature, pH of the perfusate and pressure in the aorta, hematocrit, pO_2 and pCO_2 in the perfusate, and the left ventricular pressure curve were recorded. Simultaneously with pressure record, samples of the perfusate that passed through the coronary bed were taken, with determination of glucose and lactate content, and creatine phosphokinase (CPK) activity using reagents from Human GmbH (Germany). The studies were conducted 30 min after the start of perfusion (***control group***, hereinafter referred to as 'C', n=8) and then after 3, 6, 9, 12, and 15 hours of perfusion (***experimental group***, n=8).

Statistical processing of the study results was performed on a computer using Statistica 6.0 program (Stat Soft Inc., USA). Shapiro–Wilk criterion was used to check the normality of the distribution of the obtained data. Since the hypothesis of normal data distribution was rejected, nonparametric criteria were further used. Mann–Whitney criterion was used to assess the differences between two independent samples of the control and experimental groups, and Wilcoxon criterion was used to assess the differences in the experimental group during perfusion. The data are presented as the median (Me), lower (LQ), and upper (HQ) quartiles: Me [LQ; HQ]. The critical level of significance in testing statistical hypotheses was taken to be 0.05.

RESULTS

Restoration of heart activity and HR. With the start of normothermic extracorporeal perfusion, spontaneous restoration of the heart activity was observed with stabilization of the main parameters of contractile and rhythmic function within 30 minutes, which evidences the elimination of the reversible disorders in the heart function caused by the procedure of its explantation and preparation. During the period of stabilization of cardiac function, no reperfusion disturbances of rhythm and conduction were observed. During the entire period of perfusion of isolated hearts, sinus rhythm was recorded on the electrocardiogram at a sufficient rate.

After 30 minutes of perfusion and stabilization of the heart function, HR was 285.0 [278.5; 294.5] min-1 throughout the entire period of perfusion, HR remained within physiological values without statistically significant changes; after 12 and 15 hours of perfusion, a tendency to some decrease in HR was noted (Figure 2).

Temperature, pH and pressure in the aorta. After preparation in cooled Krebs-Henseleit solution, the hearts were reperfused in the developed setup at 37°C; during perfusion, the temperature remained constant and was maintained using a circulation thermostat. The pH level was adjusted by additional introduction of sodium hydrocarbonate into the perfusate and remained stable within the physiological values of pH=7.3–7.4 during perfusion (Table 1). Perfusion of the hearts was performed at pressure in the aorta 70 mm Hg, which was monitored using a pressure sensor.

Evaluation of contractile function of heart. After stabilization of the heart function, the left ventricular systolic pressure (LVSP) was 96.0 [93.7; 98.5] mm Hg and remained without significant changes throughout 12 hours of perfusion; after 15 hours of perfusion, a 15.0% decrease in LVSP to 82.0 [79.5; 84.2] mm Hg was observed (p=0.01208 compared with control, Figure 3). After stabilization of the function, the left ventricular diastolic pressure (LVDP) was 4.0 [3.0; 5.0] mm Hg and remained without significant changes during 12 hours of perfusion; by 15 hours of perfusion, LVDP increased by 1.5 times to 6.0 [5.0; 7.0] mm Hg (p=0.0164 compared with control, Figure 4).

Assessment of biochemical markers of myocardial metabolism and myocardial damage. During the experiment, biochemical markers in the perfusate after 30 minute of perfusion and stabilization were determined at the level of physiological values without significant dynamics during 12 hours of perfusion: glucose consumption was 80.5 [70.2; 85.5] μmol/(kg×min×mmHg); lactate excretion was 35.7 [32.5; 44.2] μmol/(kg×min×mm Hg); CPK leakage was 95.8 [93.7; 111.3] IU/l, *which indicates the preservation*

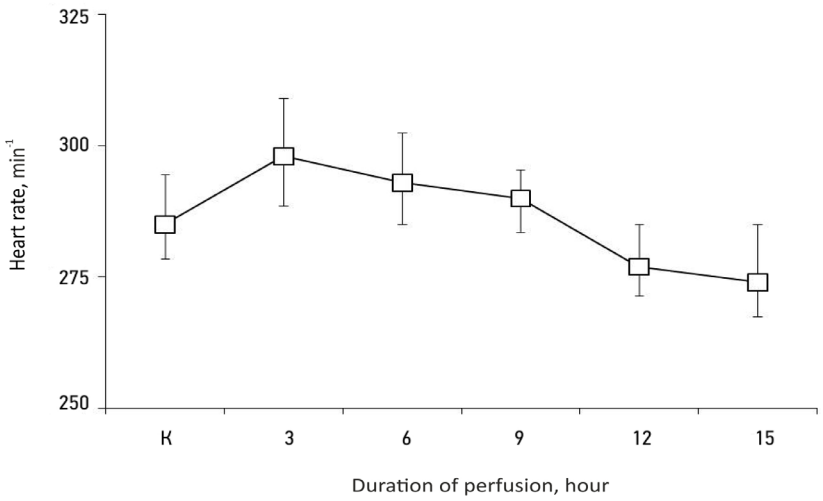

Fig. 2. Heart rate dynamics during extracorporeal perfusion of a rat's heart: К — data of the control group; 3, 6, 9, 12, 15 — data of the experimental group at 3, 6, 9, 12, 15 hours respectively.

Table 1. Parameters of normothermic extracorporeal perfusion of rat's heart

Parameters	Value
Duration of perfusion, h	12.0
Perfusion temperature, °C	36.8–37.0
Perfusion pressure, mm Hg	70±2
Perfusate pH	7.3–7.4
Hematocrit	0.30–0.35
pO_2, mm Hg	170–250
pCO_2, mm Hg	35–40

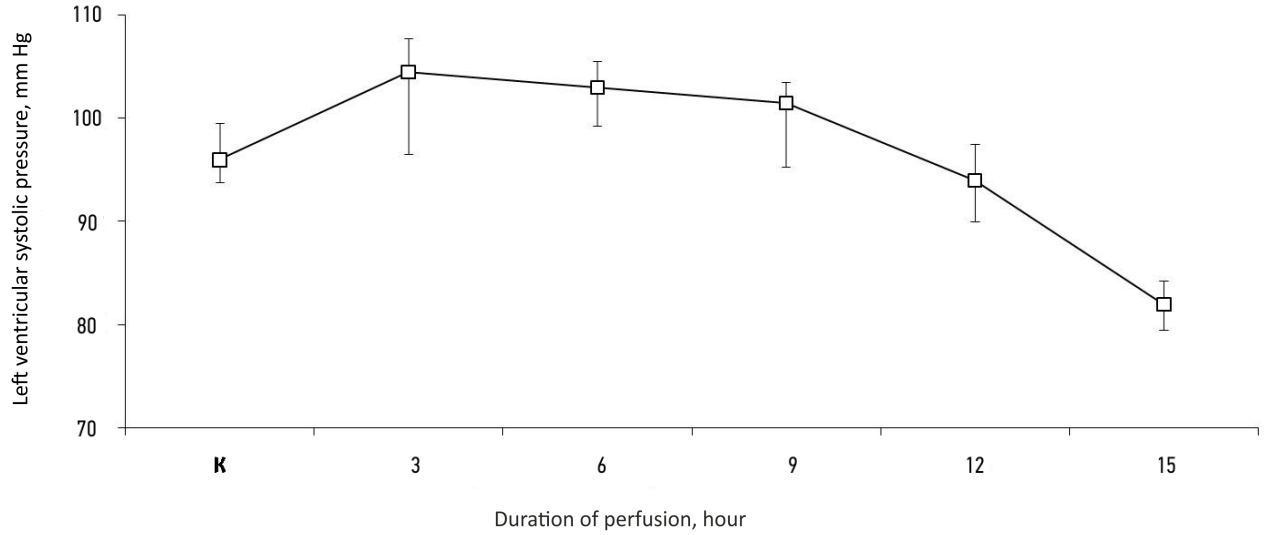

Fig. 3. Dynamics of left ventricular systolic pressure during extracorporeal perfusion of a rat's heart: К — data of the control group; 3, 6, 9, 12, 15 — data of the experimental group at 3, 6, 9, 12, 15 hours respectively.

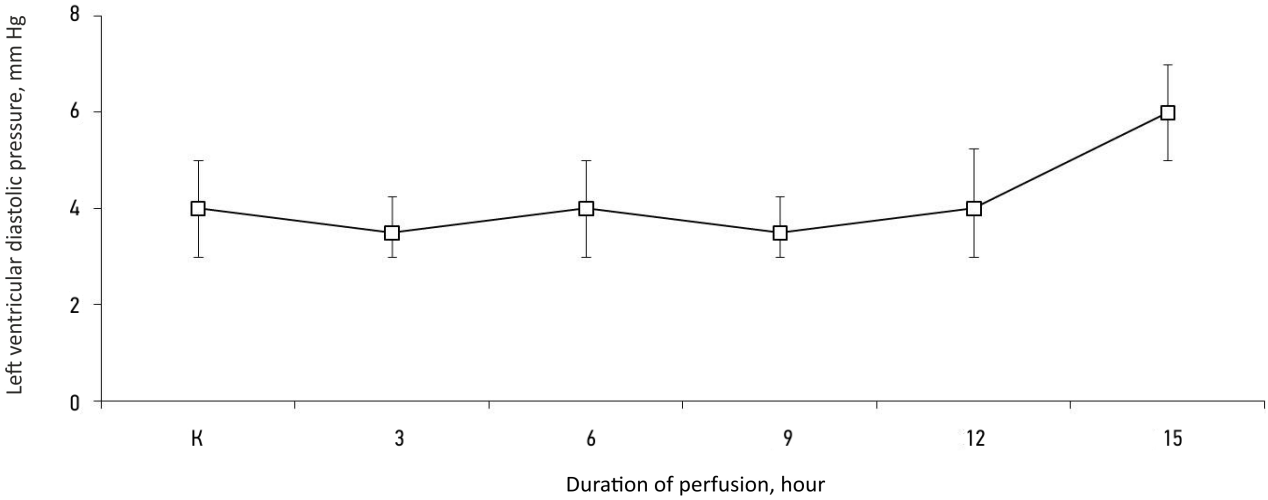

Fig. 4. Dynamics of LVDP during extracorporeal perfusion of a rat's heart: K — data of the control group; 3, 6, 9, 12, 15 — data of the experimental group at 3, 6, 9, 12, 15 hours respectively.

of cellular mechanisms of aerobic metabolism and glucose utilization, as well as the structural integrity of cardiomyocyte membranes at these perfusion periods.

After 15 hour of perfusion, the level of glucose consumption by isolated hearts per unit of function performed increased significantly up to 136.8 [130.5; 145.7] μmol/(kg×min×mm Hg, *p*=0.01208 compared with control); lactate release and CPK leakage into the perfusate increased to 58.2 [55.7; 67.4] μmol/(kg×min×mm Hg, p=0.02144 compared with control) and 229.7 [215.8; 242.4] IU/l (*p*=0.01208 compared with control), respectively, which can be explained by hypoxic changes developing in cardiomyocytes, activation of anaerobic glycolysis and increased permeability of cell membrane structures.

DISCUSSION

Given the level of development of medical technology, non-perfusion hypothermic preservation (NPHP) remains the main generally accepted method of preserving donor organs in clinical practice. With NPHP, a donor heart is washed with a preservation solution, retrieved from the donor's body, stored in the preservation solution at 4°C and transported to the clinic, where it is transplanted to the recipient [16]. With this method of preservation, the maximal period of anti-ischemic protection of the myocardium is 4–6 hours, since prolonged cold ischemia inevitably leads to progressive reduction of the transplant viability potential. Other significant disadvantages of NPHP are the absence of organ-protective effect of deep hypothermia in the case of using transplants from donors with expanded criteria and donors with irreversible circulatory arrest, as well as the impossibility of a dynamic assessment of the functional-metabolic state of the donor organ in real time to identify pathological changes caused by ischemia-reperfusion [16, 17].

In our study, the results of experimental testing of the device for perfusion preservation of the donor heart are presented. Experiments conducted on 16 intact isolated hearts of outbred male rats, demonstrated high efficiency of normothermic conditioning of the heart in the developed device for up to 12 hours, as well as the technical possibility of assessing the contractile function and metabolic processes in the myocardium in real time. The studied parameters of the functional state of the donor heart were within the physiological values for up to 12 hours, which can be characterized as normal functioning of the transplant. By 12 hours of perfusion and further, the appearance and increase of ischemic and dystrophic changes in the myocardium and, as a consequence, the development of transplant dysfunction, were noted. Perfusion parameters such as temperature, pH of the perfusate and pressure in the aorta were controlled and remained within the physiological values without significant fluctuations during the perfusion process.

It becomes evident that prolonged ex vivo device-controlled perfusion of donor organs is a demanded and promising technology for preserving donor organs, despite the difficulties of its implementation. Perfusion preservation methods ensure anti-ischemic transplant protection through oxygenation and supply of myocardium with the necessary oxidation substrates, as well as removal of end products of metabolism. The currently available data indicate that machine perfusion can become a real alternative to NPHP in clinical practice in the near future; this technology is already used to procure donor liver, kidneys, lungs and hearts [5, 18].

The use of machine perfusion will allow to increase the donor heart pool by 15.0–20.0% due to expansion of criteria for use, preservation and restoration of the viability of donor organs that could not be used previously. Taking into account a significantly high cost of perfusion preservation technologies, the overall cost savings of the healthcare system can be achieved at the expense of reduction of the number of re-hospitalizations of patients with decompensated heart failure [19].

Our study was of pilot character and was conducted on a limited sample to determine the principal possibility of anti-ischemic protection of the donor heart in the developed perfusion device during the experiment. The next stages of the study, as we see it, will be an in-depth investigation of the contractile function, metabolism and histostructure of the myocardium, the function of the coronary endothelium, assessment of the dynamics of free radical oxidation in the myocardium after prolonged normothermic extracorporeal perfusion in the experiment.

The developed perfusion complex can be a technological platform for a comparative analysis of the effectiveness of cardioprotection methods in different parameters of heart perfusion. However, to extrapolate the experimental data and determine the possibilities of introducing perfusion preservation methods in clinical transplantology, continuation of fundamental investigation on larger laboratory animals-biomodels and further development of hardware-software complex with consideration of anatomical and physiological characteristics of a human heart are required.

CONCLUSION

The results of experimental testing of the developed original device for perfusion preservation of donor hearts on outbred rats showed that normothermic perfusion allows for maintaining the viability of an isolated contracting heart for 12 hours in conditions maximally close to physiological ones, and also to conduct a dynamic assessment of the functional and metabolic state of the organ.

ADDITIONAL INFORMATION

Author contributions. P.A. Ermolaev — concept and design of study, collection and processing of material, analysis of data, writing the text; T.P. Khramykh — scientific guidance, concept and design of study, editing; L.O. Barskaya — concept and design of study, collection and processing of material, analysis of data, writing the text. All authors approved the manuscript (the publication version), and also agreed to be responsible for all aspects of the work, ensuring proper consideration and resolution of issues related to the accuracy and integrity of any part of it.

Ethics approval. The study was approved from the Ethics Committee of the Omsk State Medical University (Protocol No. 12 of November 24, 2021).

Consent for publication. All participants of study voluntarily signed an informed consent form before being included in the study.

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