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FIRST RUSSIAN EXPERIENCE IN LIVER AND KIDNEY TRANSPLANTATION FROM DONORS WITH OUT-OF-HOSPITAL CARDIAC ARREST: 3 YEARS' RESULTS

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Introduction. In megacities, the use of organs obtained from those who died as a result of sudden out-of-hospital cardiac arrest (OHCA) for transplantation is one of the promising ways of addressing the problem of organ donor shortage. In St. Petersburg, the model of transition from life support via extracorporeal membrane oxygenation (ECMO) of patients after OHCA to ECMO life support for organs of potential donors was tested for the first time. **Materials and methods.** In order to implement the program, round-the-clock ECMO and transplantation teams were organized at the inpatient emergency ward of Pavlov First St. Petersburg State Medical University. Interaction with the St. Petersburg City Emergency Station, St. Petersburg was established. The protocol of work with potential donors brought to the hospital after a sudden circulatory arrest was developed, approved by the ethics committee, and implemented in clinical practice. This was the first in Russia and in international practice. Between 2017 and 2020, 67 patients with sudden OHCA were brought to the inpatient emergency ward. In 4 (5.97%) cases, advanced cardiovascular life support was successful, and 11 (16.42%) patients became effective donors. Mortality among this group of patients without subsequent postmortem donation was 77.61% (52 patients). **Results.** Liver transplantation from non-heart-beating donors (NHBDs) whose blood circulation was restored by ECMO (ECMO NHBD) was performed in 5 recipients who were in severe condition against the background of liver failure. In 1 (20%) case, there was severe liver allograft dysfunction for 33 days with subsequent complete restoration of function. Kidney transplantation was performed in 22 patients. Immediate graft function occurred in 10 (45.45%), while delayed function occurred in 12 (54.55%) patients. Kidney graft survival was 86.4%, kidney graft recipient survival was 95.5%, liver graft recipient survival was 80%, and the follow-up period was 24.1 ± 7.15 months. **Conclusion.** The use of ECMO to save the lives of patients with sudden OHCA can be implemented in conditions of a high degree of organization and synchronization of the work of the city emergency medical station and the emergency department of a multidisciplinary hospital. If cardiopulmonary resuscitation with ECMO (ECMO CPR) fails, it is possible to launch the ECMO NHBD donor program. Long-term outcomes of liver and kidney transplantation from ECMO NHBD are consistent with those using organs from brain-dead donors. Widespread implementation of the new organ donation model will increase the availability of transplant care.

Keywords: out-of-hospital irreversible cardiac arrest donors, non-heart-beating donors, extracorporeal membrane oxygenation, ECMO CPR, ECMO NHBD, liver transplantation, kidney transplantation.

INTRODUCTION

The main focus of modern transplantology is the development of new strategies for solving the problem of donor organ shortage [1–3]. The use of organs obtained from those who died as a result of sudden out-of-hospital cardiac arrest (asystolic donors, ASD) is one of the promising directions in solving this problem [4, 5]. Our own [6] and European experience with the use of protocols for working with ASD have shown the effectiveness and no significant differences in the outcomes of transplants, compared to the results of kidney transplants obtained from brain-dead donors [7–10].

Extracorporeal membrane oxygenation (ECMO) for emergency restoration of blood circulation is an invasive method of extracorporeal cardiopulmonary resuscitation (ECPR), which was proposed for patients with cardiac

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arrest in order to restore and maintain blood circulation in the body during cardiac arrest [11, 12]. ECMO has been used in cardiac arrest since 1976 with the introduction of the battery-powered portable cardiopulmonary bypass machine [13]. The use of this circulatory restoration method for a number of years was limited to the use only in certain groups of patients: after open-heart surgery, subjected to profound hypothermia and drug overdose [14–16]. Miniaturization of extracorporeal circulatory restoration devices, the use of perfusion circuits with heparinized coating and methods of percutaneous cannulation of main vessels have made it possible to expand the clinical range of application of this method [17–21]. Clinical studies have shown the effectiveness of early ECMO to improve prognosis in patients with prolonged cardiac arrest occurring both in inpatient (in-hospital cardiac arrest) and out-of-hospital conditions (out-of-hospital cardiac arrest) [22–23].

Guidelines by the International Liaison Committee on Resuscitation explicitly state that ECMO can improve outcomes in patients with cardiac arrest, compared with the standard cardiopulmonary resuscitation (CPR) protocol, in cases of cardiogenic shock and cardiac arrest, where cardiac pathology is known from history to be amenable to immediate invasive correction [24]. The American Heart Association has proposed that ECPR should be considered as a care option for inpatients with cardiac arrest in period that there is no blood flow is minimal and the condition that led to cardiac arrest is reversible (for example, hypothermia or drug intoxication) or treatable by myocardial revascularization or heart transplantation [25]. In any case, the use of ECMO in clinical practice presupposes the adoption of rather complex medical decisions in situations where the patient is in critical condition and his rescue fully depends on the success of the medical team.

The effectiveness of ECMO in reviving patients with cardiac arrest explains the reason why it is also used for donor programs. The most famous is the so-called "Spanish protocol" – donors from the streets – successfully implemented in major cities of Spain [1, 27, 33].

Ischemia-reperfusion injury inevitably accompanies the process of obtaining donor organs from ASDs. Pathophysiological processes occurring during ischemia-reperfusion can be minimized by consecutive application of indirect automatic cardiac massage and switching to restoration and maintenance of blood circulation in the deceased patient using ECMO. This has been demonstrated in some of our previous works [6, 32, 50].

This paper presents the 3-year outcomes of organ transplantation from donors with out-of-hospital irreversible cardiac arrest.

MATERIALS AND METHODS

Actions by ambulance teams were based on the organizational protocol primarily aimed at saving the life of a patient with sudden out-of-hospital irreversible cardiac arrest, which was approved by the local ethics committee of Pavlov University (Protocol No. 46 dated September 22, 2017). Discussion and approval of the protocol was agreed with City Ambulance Station, St. Petersburg. Taking into account the radical influence of time on outcomes of resuscitation measures, work involved those ambulance substations of Petrogradsky district of St. Petersburg, whose area of responsibility included the territory near Pavlov University.

According to the protocol, upon arrival, the ambulance team performed a set of resuscitation measures on the patient with sudden cardiac arrest, including the connection of Lucas II chest compression system (Jolife AB, Sweden), and mechanical ventilation (MV). Given the localization of the program within Petrogradsky district of St. Petersburg only, in cases of timely notification, the ambulance team was able to arrive to the patient and begin resuscitation measures within 7–10 (7.3 ± 4.1) minutes of receiving the call, and deliver the patient to the hospital within 50–70 (57 ± 12.8) minutes. On the background of continuing chest compressions with the help of Lucas II device, the resuscitated person was delivered to the inpatient emergency ward of Pavlov University, where in addition to the intensive care unit (ICU), an ECMO team set out for a 24-hour work to implement this program.

Each patient, depending on the specific clinical situation, was given the full range of life support procedures from the arrival of the ambulance team, and continued in the ICU of the hospital.

The ECMO protocol was initiated primarily to save the patient's life and as part of the "life support" procedures based on the criteria developed and accepted at Pavlov University (Table 1).

Under resuscitation conditions, the femoral artery and vein (arterial with "Luer-port" 17 Fr and bicaval venous 30/33 Fr cannulae) were cannulated by puncture, under ultrasound control or "openly" (Fig. 1). Connection to a prefilled perfusion circuit was performed. For ECMO, we used centrifugal pump RotaFlow (Maquet, Germany), a prototype of Ex-Stream for emergency blood circulation restoration (TransBioTech, Russia, the use of prototype portable perfusion device was approved by the local ethics committee of Pavlov University). We used perfusion tubes (Kewei, China), RotaFlow centrifuge head (both for Maquet, Germany, and for Ex-Stream, TransBioTech, Russia), membrane oxygenator (Kewei/Oxygenator Keweiadult, China), and leukocyte filter (LeukoGuard 6, Pall, Terumo, USA) (Fig. 2, 3). The circuit was initially filled with sodium bicarbonate solution, saline, colloidal solution, antibiotic, heparin sulfate, fibrinolytic, and methylprednisolone (Table 2). Accepted standard perfusion characteristics for ECMO: flow rate 2.5–3.5 L/min, mean arterial pressure 80–100 mm Hg, oxygen flow through oxygenator 3–4 L/min. Control

and correction of laboratory indicators were performed every hour.

After extended CPR measures, including ECPR, where the measures were not effective (atonic coma, wide pupils, no reaction to light, isoelectric line on an ECG when the Lucas device was stopped), death was stated according to the generally accepted criteria. In patients eligible for donation, after the 'no touch' period, 20 minutes, the deceased was injected with 10,000 U of heparin sulfate via central venous access and the ECMO procedure was resumed in order to maintain viability of the deceased organs. Thus, there was a transfer from life support procedure to the deceased donor's organ preservation procedure.

Decisions to perform organ transplantation from donors with out-of-hospital cardiac arrest and determine their suitability were based on the assessment of time parameters, ECMO effectiveness, and imaging and laboratory findings. Each patient underwent spiral computed tomography (SCT) with intravenous contrast (Ultravist 370 or Omnipack 350, 100 ml, bolus injection) to assess organ perfusion.

Absolute contraindications to the use of medical technology were taken as follows:

1. Presence of infections: HIV, HBs, HCV, RW (hemotransmissible infections were tested on Abbott Architect i2000sr automatic immunofluorescent analyzer with Abbott diagnostic kits).

Table 1

Criteria for initiating the ECMO Protocol

Pre-hospital stage	Inpatient Emergency Ward (IEW)	ECMO team
Age (18–75 years)	Re-assessment of the pre-hospital criterion set	Diameter of femoral vessels not <5.5–6 mm according to ultrasound examination
Ventricular fibrillation or ventricular tachycardia (VF/VT) without electro-pulse therapy effect (at least three discharges)	Exhaled CO_2 (on arrival at the IEW) >10 mmHg	Time from the moment the ambulance team is called to the moment the patient on the IEW table is about 60 minutes
Received Amiodarone 300 mg	PaO_2 >50 mmHg or O_2 Sat >85%	Synchronization with Lucas machine if IEW criteria do not meet the setting up and connection of femoral cannulas against the background of CPR
Technical ability to connect the Lucas device	Lactate <15 mmol/L	Transfer to the Department of X-ray surgical methods of diagnosis and treatment, assessment of angiography results
Absence of incurable diseases (Stage 4 cancer, end-stage liver, kidney, heart disease, etc.)		
Information about refusal to do intubation and CPR		
No ongoing bleeding No injuries		

Fig. 1. Connection of ECMO device to the donor femoral vessels (prototype of portable perfusion pump Ex-Stream) in the conditions of X-ray endovascular diagnostics and treatment room

2. Information about kidney disease, liver disease, malignant tumors, purulent inflammatory processes in abdominal cavity and retroperitoneal space, generalized infections;
3. Presence of direct or indirect evidence of drug use (traces of injections, tattoos, anamnestic indications, etc.);
4. Severe atherosclerosis of the donor's peripheral vessels, which precludes adequate perfusion;
5. Violation of the integrity of the donor's vascular bed, ongoing bleeding, massive blood loss;
6. More than 4 days of ECMO procedure after CPR (signs of multiple organ failure);
7. Macroscopic changes in the donor organ, excluding its subsequent use for transplantation (signs of thrombosis, marked cyanosis, stony density, etc.);
8. Lack of satisfactory organ perfusion in SCT angiography (Fig. 3).

Relative contraindications to donation were developed and adopted in the form of a point system (5 or more points – donor refusal):

1. The period from cardiac arrest to the beginning of resuscitation measures by the emergency medical team (more than 20 minutes) (1 point);
2. Warm ischemia period ≥120 min (mechanical chest compressions before the onset of ECMO), pO_2 less than 50 mmHg (1 point);
3. Presence of expanded donor criteria: age (over 50 years old), diabetes mellitus, hypertension, history of arterial hypertension, systemic diseases (psoriasis, autoimmune diseases), etc. (1 point for each condition);
4. Diagnosed damage to abdominal organs, retroperitoneal space (1 point);
5. Proteinuria, pyuria, macrohematuria, bacteria, fungal spores in urine sediment (1 point);
6. Absence of diuresis for 2 or more hours (1 point);
7. Serum creatinine level – 0.25 mmol/L or higher (1 point);
8. Being in the "red zone" for more than 6 hours and in the ICU for more than 72 hours (1 point).

After the donor's organs were found to be preliminarily suitable for explantation, and permissions were obtained from a forensic medical expert and the hospital management, the donor was taken to the operating room. Under continuing ECMO, laparotomy was performed, the aorta, iliac vessels, and inferior vena cava were isolated. The isolated abdominal region was cold perfused with Custodiol solution (Dr. Franz Kohler Chemie GmbH, Germany, temperature 4 °C, 15 liters) through luer-port of arterial cannula previously used for ECMO. Then the kidneys and liver were removed according to standard technique.

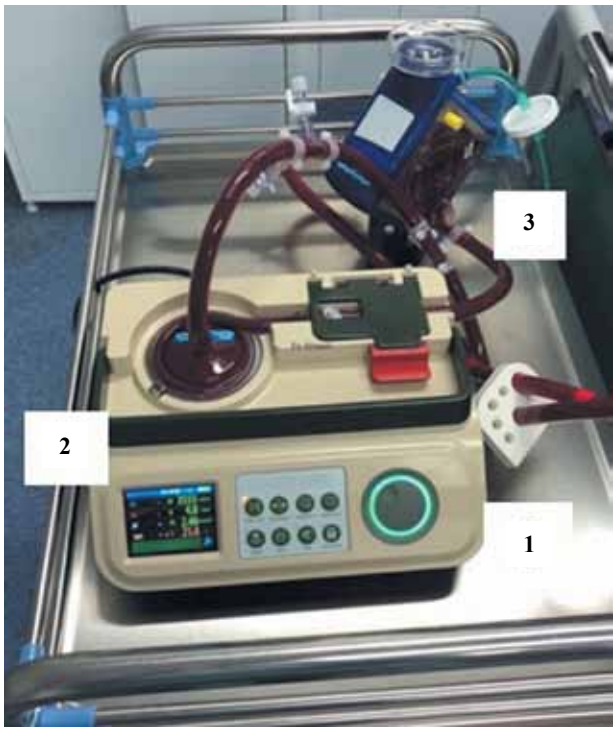

Fig. 2. General view of ECMO donor perfusion circuit (1 – prototype of Ex-Stream, 2 – centrifugal head, 3 – oxygenator and arterial filter) in the "red zone" of the inpatient emergency department

Kidney allotransplantation and orthotopic liver transplantation from donors with sudden out-of-hospital circulatory arrest were performed using standard hospital-accepted surgical techniques, medication and immunosuppressive therapy regimens.

Table 2

Primary filling of the EKMO contour

Group of drugs	Drugs used according to the protocol	Dosage (volume)
Crystalloid solutions	Sodium chloride 0.9%	Contour filler base
	Sodium bicarbonate 5%	200 ml
Colloidal solution	Gelofusine	500 ml
Fibrinolytic	Streptokinase	1.5 million units
Antibiotic	Cefazolin	2.0 g
Anticoagulant	Heparin sulfate	10000 U
Methylprednisolone	Solu-Medrol	1000 mg

CLINICAL EXAMPLE

Female patient N., 27 years old, at 00:00 at a metro subway station, suddenly lost consciousness, and suffered a cardiac arrest. Chest compression was performed until the arrival of an ambulance team. At the time of arrival of the medical team (00.15), she was in a state of clinical death. Prolonged CPR (electro-pulse therapy 200 J #5, connection of Lucas 2 (Sweden) resuscitation machine for chest compression, MV, adrenaline 12 ml total, cordarone 400 mg) was performed. Against the background of continuing mechanical chest compression, the patient was delivered to the in-patient emergency ward, 62 minutes after cardiac arrest. The patient's initial data: height 165 cm, weight 60 kg, lactate – 15 mmol/L, hemoglobin 107 g/L, pO_2 – 37 mmHg, pCO_2 55.6 mm Hg, atonic coma, isoelectric line in ECG (when the Lucas II machine was off). Given persistent asystole, atonic coma, lactate value over 15 mmol/L in accordance with the ECMO protocol, CPR was not included in the scope of measures. After a full CPR complex within 30 minutes, chest compressors were turned off, and biological death was stated (01.32).

After 20 minutes from the moment of confirmation of biological death, taking into account the possibility of implementing the organ donation protocol, the Lucas II device was resumed. Cannulation of the right femoral vessels was performed under ultrasound control, ECMO perfusion was initiated. Perfusion characteristics: flow rate 2.5–3.5 l/min, mean arterial pressure 85–105 mmHg, oxygen flow through oxygenator 3–4 l/min.

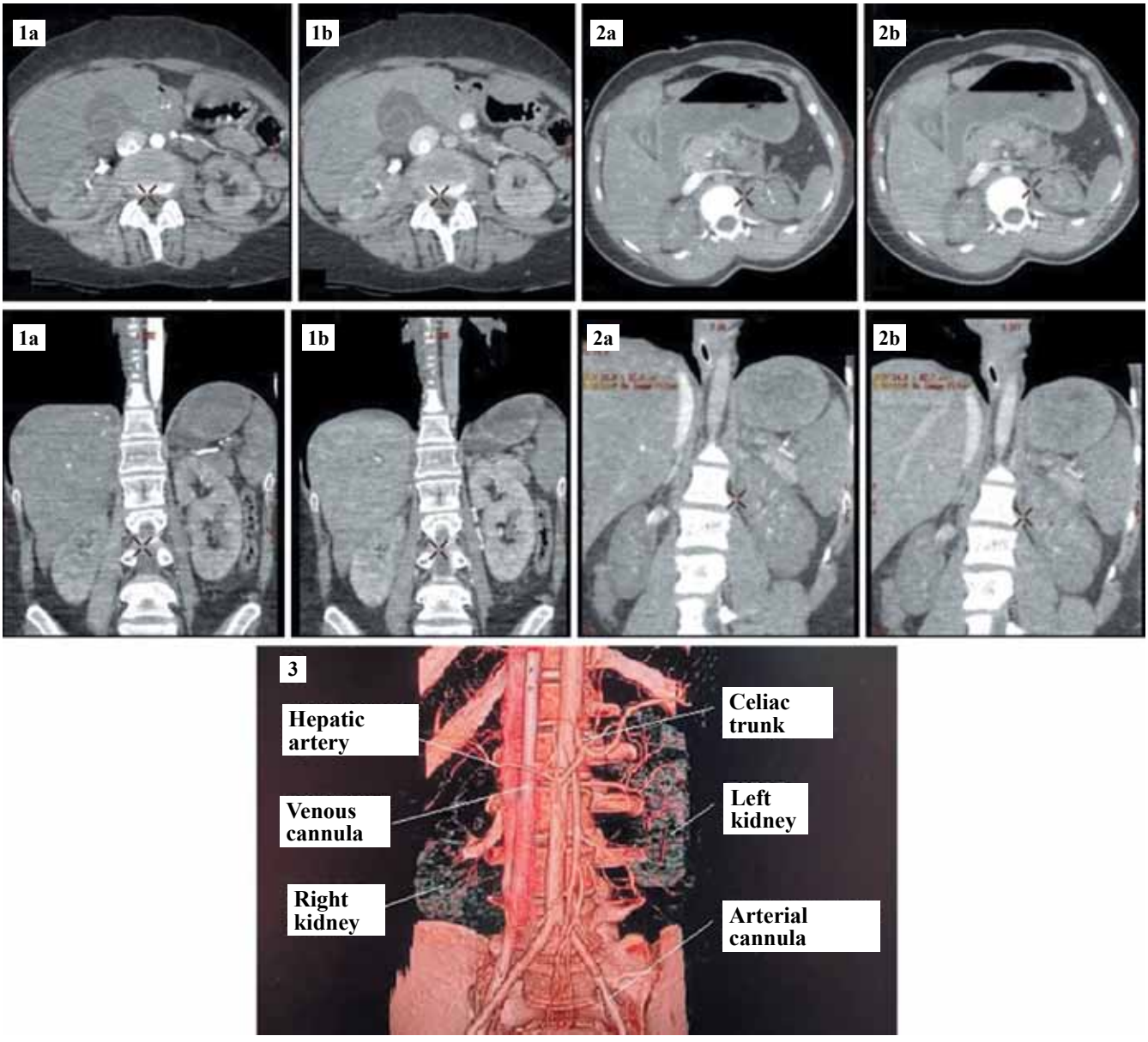

Fig. 3. Results of intravenous contrast-enhanced CT in a potential donor during ECMO (1 – satisfactory perfusion of the liver, kidneys (1a – arterial phase, 1b – venous phase); 2 – no perfusion (1a – arterial phase, 1b – venous phase); 3 – 3D reconstruction, arterial phase, satisfactory perfusion of abdominal region)

Examination against the background of ECMO revealed no contraindications to donation (2 points according to the accepted relative contraindication scale), the organs were found to be preliminarily suitable for transplantation. After obtaining the permission of a forensic medical expert and hospital administration, the liver and two kidneys were extracted in the operating room according to the accepted technique. ECMO lasted for a total of 343 minutes.

A 55-year-old female patient M. became the liver recipient. She was diagnosed with chronic unverified hepatitis with an outcome in liver cirrhosis. Child-Pugh class C. MELD 19. Portal hypertension, grade 2 esophageal varices. Ascites. Hepatic encephalopathy. The operation was performed according to the standard Piggy-Back technique. Liverless period – 50 min, secondary warm ischemia time – 30 min, cold ischemia time – 435 minutes. Graft function was immediate. Drains were removed on days 4 and 5 after the operation. She was transferred to the ward on day 5 after transplantation. Duration of hospitalization was 23 bed-days, the patient was discharged with a satisfactorily functioning graft. Laboratory indicators 18 months after transplantation: AST 35 U/L, ALT 41 U/L, bilirubin 19 μmol/L.

Transplantation operations for the obtained kidneys were performed sequentially in immunologically compatible recipients.

1. *Patient R., 27 years old, diagnosed with "chronic glomerulonephritis, morphologically unverified. Nephrosclerosis. Renal replacement therapy by long-term hemodialysis since 2016". There was delayed graft function, 6 hemodialysis procedures were performed. The patient was discharged on day 24 with a satisfactory functioning graft. Laboratory indicators 18 months after transplantation: creatinine 0.189 mmol/L, urea 10.8 mmol/L.*
2. *Patient P., 34 years old, diagnosed with "chronic glomerulonephritis, morphologically unverified. Nephrosclerosis. Renal replacement therapy by long-term hemodialysis since 2007". There was delayed graft function, 1 hemodialysis procedure was performed. The patient was discharged on day 24 with a satisfactory functioning graft. Laboratory indicators 18 months after transplantation: creatinine 0.169 mmol/L, urea 11.2 mmol/L.*

STUDY RESULTS

Between 2017 and 2020, the program delivered 67 patients with out-of-hospital cardiac arrest, who were brought to the emergency ward within the framework of the program. In 4 (5.97%) cases, life-saving extended CPR and ECMO interventions were effective (patients were discharged without neurological deficit), 11 (16.42%) became effective donors. The mean age of the patients with out-of-hospital cardiac arrest was 50.3 ± 16.7 years. The pattern of outcomes of extended CPR and ECMO is shown in Fig. 4.

Kidney transplantation from the mentioned donors was performed in 22 patients. The mean age of the recipients was 46.8 ± 11.6 years. The time from the onset of cold perfusion to graft reperfusion was 570.4 ± 179.6 minutes, secondary warm ischemia lasted for 34.2 ± 6.42 minutes. Immediate graft function occurred in 10 (45.45%) cases. There was an average of 4.2 ± 3.2 hemodialysis procedures in cases of delayed graft function. Kidney graft function was restored on day 12 to 15. In 2 (9.1%) cases of kidney transplantation, the graft was removed due to acute rejection crisis and renal vein thrombosis during the first 3 days after transplantation.

Liver transplantation was performed in 5 patients with cirrhosis of various etiologies (autoimmune hepatitis, primary sclerosing cholangitis, chronic viral hepatitis C, etc.) in severe condition caused by end-stage liver failure and its complications (severe hepatic encephalopathy, portal hypertension, etc.). The mean age of the patients was 55.4 ± 10.1 years, MELD value 18.6 ± 7.9, Child-Pugh class C. The average cold and warm ischemia times were 380 ± 36.7 and 52 ± 10.3 minutes, respectively. There was 1 (20%) case of severe graft dysfunction within 33 days after transplantation, followed by complete restoration of graft function. One death was due to total thrombosis of the portal vein and hepatic artery on day 2 after transplantation in a patient

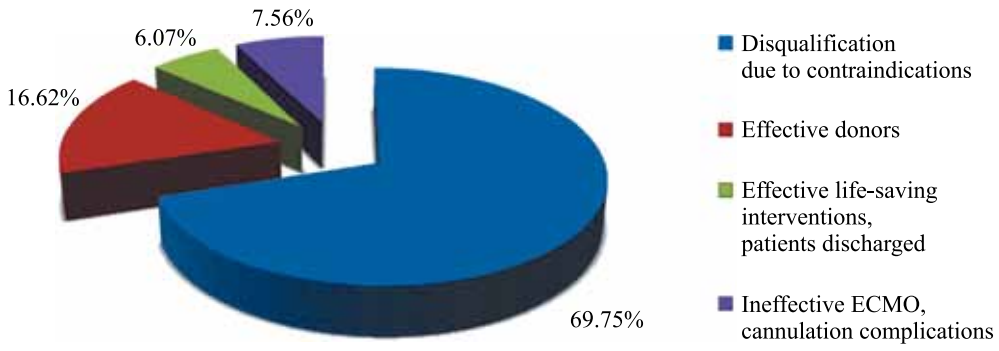

Fig. 4. Structure of results of advanced ECMO CPR

with hepatocellular cancer against the background of chronic viral hepatitis C.

The follow-up period of the organ recipients from ASD was from 14 to 34 (24.1 ± 7.15) months. Graft function during the follow-up period was satisfactory. The dynamics of the main laboratory indicators reflecting the graft function are shown in Figs. 5–8.

Among late complications (in the period from 1 to 34 months after transplantation), the frequency of kidney transplant and liver transplant rejection crises were 10% (2) and 25% (1), respectively. Liver rejection crisis was caused by the patient's violation of immunosuppressive therapy regimen; it was successfully treated with glucocorticoids. Among the late complications of liver transplantation, ischemic stricture of biliary anastomosis also occurred in one case. Endoscopic stenting of the anastomosis area was performed. Early and late complications of kidney and liver transplantation are presented in Table 3.

The survival rates of kidney grafts, renal transplant recipients, and liver transplant recipients were 86.4%, 95.5% and 80%, respectively (Fig. 9). One kidney transplant recipient died 23 months after transplantation due to severe COVID-19.

DISCUSSION

In Spain, asystolic donors account for 24% to 28% of donor activity, depending on the center [33]. In Russia and other countries, patients with sudden out-of-hospital cardiac and respiratory arrest for whom resuscitation

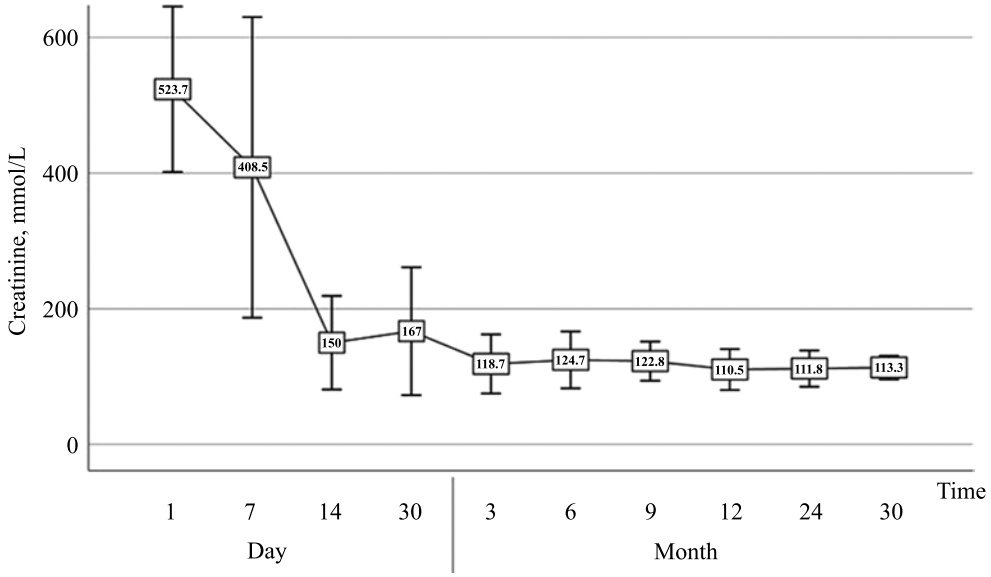

Fig. 5. Dynamics of mean creatinine levels during the follow-up period for kidney transplant recipients (95% CI)

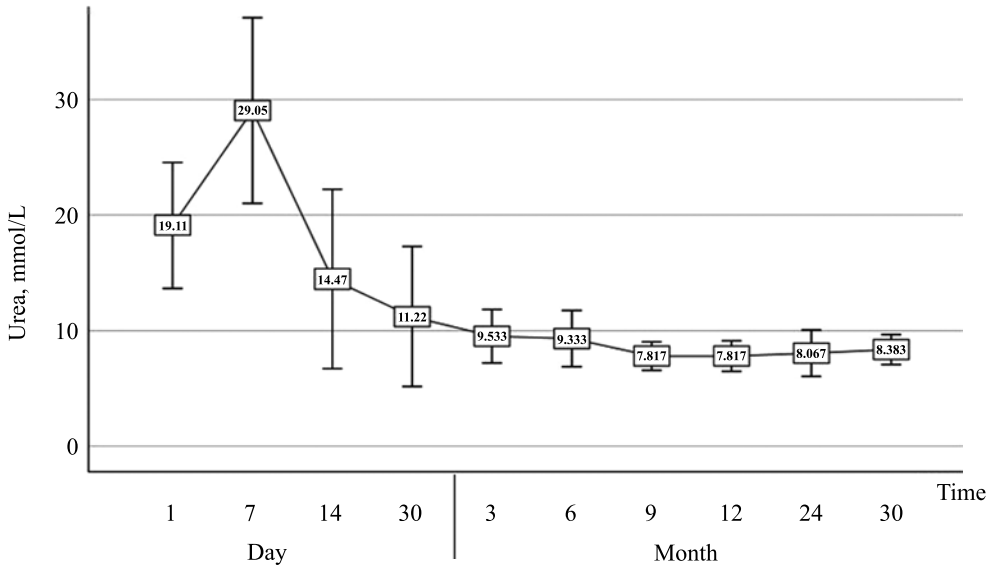

Fig. 6. Dynamics of mean urea levels during the follow-up period for kidney transplant recipients (95% CI)

attempts have been unsuccessful can also be considered as potential donors [34]. The novelty of donor service is in rapid interaction between the transplantation team and specialists trying to save the life of patients with sudden out-of-hospital cardiac arrest using a combination of conventional resuscitation and emergency use of ECMO. On one hand, having a life-support system in the emergency ward can increase the survival of patients whose resuscitation would not even have been performed in the past, and in cases of ineffective life-saving measures, minimize ischemic injury to the organs of those who have thus become donors, and initiate a transplantation program [6, 26–27].

In our case, the most significant seems to be the problem of determining the possibility of transition from "resuscitation measures" to the "donor protocol" (for example, how to ascertain the death of a person whose heart is not working, but blood circulation is preserved due to the use of an external mechanical support device; can we use the classical "brain death" criteria to establish the death of a patient who is on "assisted" circulation). It is necessary to further improve perfusion programs to save the lives of patients, both in cases of sudden cardiac arrest, and waitlisted patients with end-stage chronic diseases [26, 27].

Out-of-hospital asystolic donors are subjected to at least two critical non-circulation periods (from cardiac

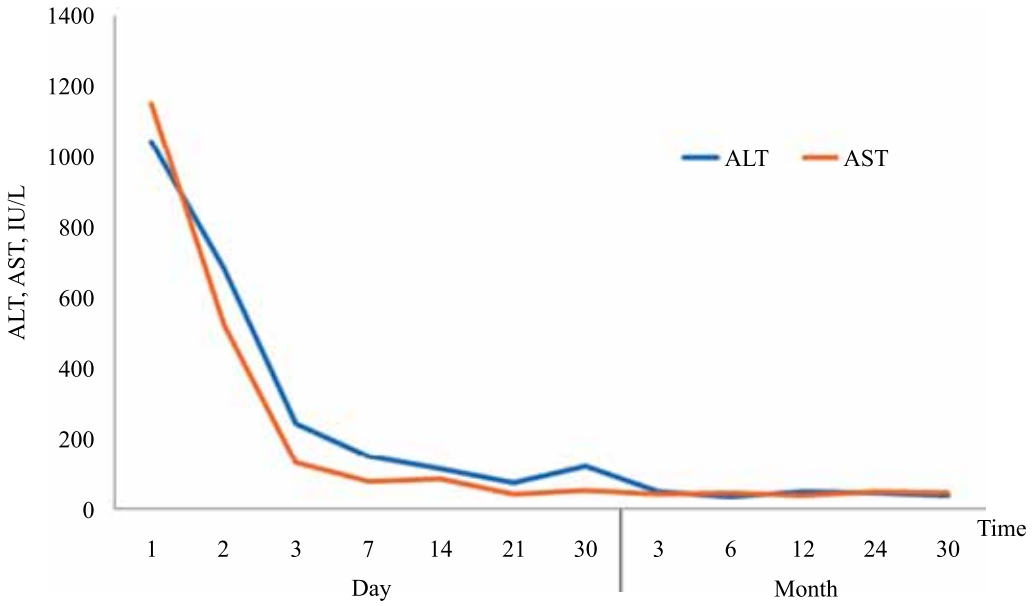

Fig. 7. Dynamics of mean values of ALT, AST (U/L) during the follow-up period for liver transplant recipients

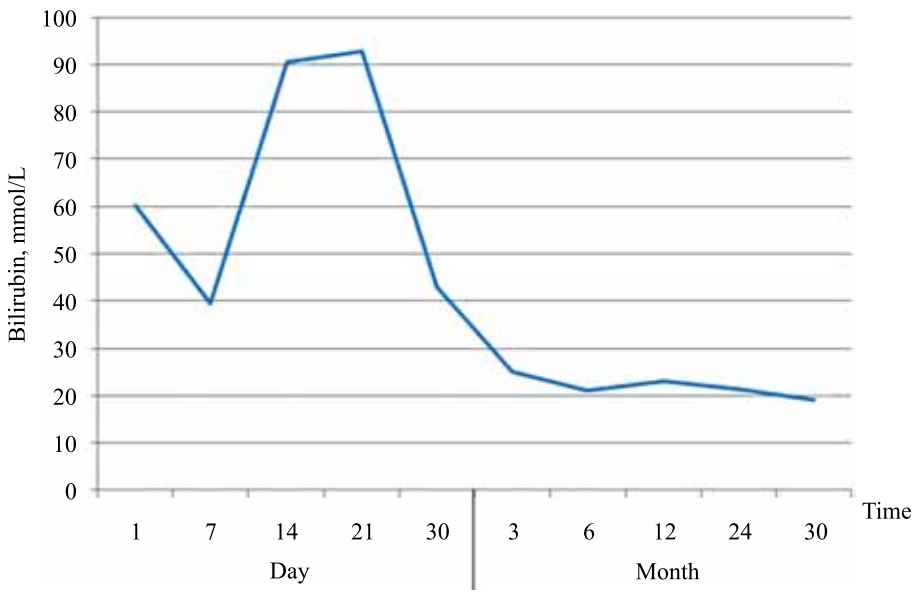

Fig. 8. Dynamics of mean bilirubin levels (μmol/L) during the follow-up period for liver transplant recipients

arrest before resuscitation and during the 'no touch' period, or the so-called "inactivity" period), whose duration, in turn, determines the fundamental possibility of using their organs and has a significant impact on outcomes of subsequent transplants [35].

All mechanical techniques for blood circulation resumption in the donor's body can be called by a common term "extracorporeal membrane oxygenation" (ECMO), or, more precisely, "extracorporeal life support", in our case – *restoration and maintenance of organ life in the body of a deceased person*.

There is a steady tendency to use devices for stage-by-stage ex vivo perfusion for diagnosis, selection and treatment for organs obtained from this category of donors [28–31].

The time interval from the moment of cardiac and respiratory arrest to the beginning of resuscitation measures should be considered as one of the most important factors influencing the effectiveness of both the programs of care for patients with sudden out-of-hospital circulatory arrest and out-of-hospital organ donation. Only CPR performed by emergency physicians or using external mechanical systems for chest compressions (device-assisted CPR) should be considered. Thus, if this interval was more than 20 minutes or its duration was not known, such patients were not considered as potential donors in the Pavlov University protocol. According to our data, the average duration of such an interval was 7.5 ± 2.4 minutes. In the Italian and Spanish ASD protocols available to us, this period was not more than 15 minutes [36].

In some countries, implementation of this donor protocol is limited by the very possibility of performing any manipulations with the body of the deceased after confirmation of biological death. In Spain and the United

Table 3

Complications of kidney, liver transplantation from NHBDs

	Liver transplant (n = 5)	Kidney transplant (n = 22)
Graft function:		
Delayed	1 (20%)	10 (45.45%)
Immediate	3 (60%)	10 (45.45%)
Early complications (within 1 month after transplantation):	n = 5	n = 22
Graft vascular thrombosis	1 (20%)	1 (4.55%)
Acute graft rejection crisis	–	1 (4.55%)
Long-term early graft dysfunction	1 (20%)	1 (4.55%)
Mortality	1 (20%)	–
Late complications (1–34 months after transplantation)	n = 4	n = 20
Graft rejection crisis in time	1 (25%)	2 (10%)
Biliary anastomotic stricture	1 (25%)	–
Mortality	–	1 (5%)

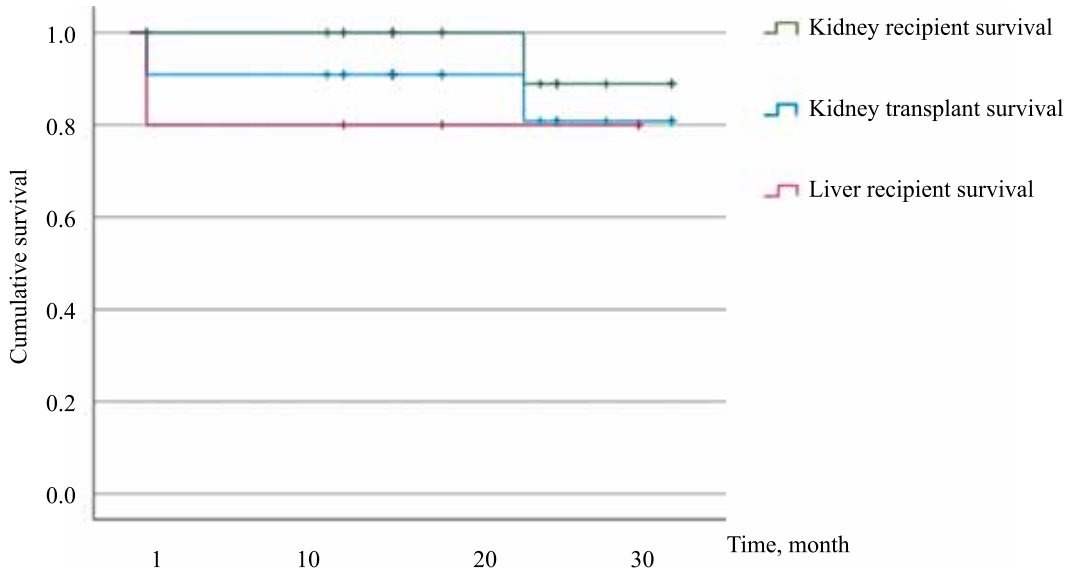

Fig. 9. Cumulative survival of kidney transplants and recipients who received donor organs from NHBDs (95% CI)

States, it is required to obtain the consent of relatives to perform femoral cannulation for the purpose of donation after the death of the person, which in some cases significantly complicates the implementation of the protocol (inability to contact relatives or lack of communication with relatives for a long period of time) [37]. Thus, in the so-called New York protocol, transportation of a potential donor to a donor hospital was planned to be performed by a separate team [38]. However, in Italy, part of the manipulations, namely, puncture of the femoral vessels of the potential donor and administration of anticoagulants, can be performed already at the stage of transportation to the hospital from the scene [39]. The situation is complicated by implementation of two protocols at once: CPR using auto-mechanical systems of assisted circulation and oxygenation (ECPR) and out-of-hospital asystolic donation program. The use of additional external assisted circulatory devices in CPR until death is confirmed often creates additional difficulties in the "validation" of the potential donor, and if there are signs of resuscitation failure, it is required to confirm brain death against the background of continuing assisted circulation [40]. Although recent experience in Portugal has shown that both programs can coexist successfully [41].

Another, no less important factor is the 'no-touch' time (period of inactivity), the period from the moment cardiac arrest occurs to the moment biological death is confirmed. The 'no-touch' time varies from 2 to 20 minutes without any ECG activity on the monitor [42]. As for the Pavlov University protocol for asystolic donors, such interval is not defined and not regulated. Therefore, we accepted the highest permissible time interval of 20 minutes, which, in our opinion, excludes ethical contradictions in the issue of establishing and irreversibility of biological death of a patient when all means of resuscitation have been exhausted.

In most protocols available to us from foreign literature, the total time determined as insufficient perfusion of internal organs against the background of an automatic indirect heart massage machine is limited to 150 minutes [43, 44]. In general, analysis of international results of organ transplants from out-of-hospital donors have shown that the permissible total warm ischemia time for kidneys is up to 360 minutes, liver – up to 140 minutes, lungs – up to 240 minutes [45]. Given the insufficiency of organ perfusion during chest compressions, we designated its time as the primary warm ischemia time, it was considered as an aggravating factor, and was limited to the "permissible" 120 minutes of automatic cardiac massage.

General heparinization and cannulation of vessels for perfusion have a special place in implementation of these protocols. According to Italian authors, as mentioned earlier, the use of heparin and installation of introducers (but not cannulas) in the lumen of the femoral vessels before the patient's death is allowed [39]. Injection of anticoagulants before the moment of death is confirmed when working with this category of donors (at the stage of potential donor transportation to the hospital) is associated with possible fatal complications (intracerebral bleeding, hemothorax, intra-abdominal bleeding, etc.), which itself can stop initiation of donor protocol. Based on our experience, heparin administration before the moment of death can be justified if CPR is performed using the emergency use of ECMO assisted circulation to save the lives of patients with sudden cardiac death. At the same time, installation of introducers in the vascular lumen should be performed as early as possible, since absence of pulsation in the arteries increases the likelihood of technical errors at the stage of donor vascular cannulation. The use of mechanical cardiac compression systems and a ventilator can significantly reduce total warm ischemia time and increase graft utilization and survival [46].

Vascular cannulation prior to death makes it possible to reduce the warm ischemia time and. At the same time, this raises some ethical concerns among the foreign professional transplant community because there is the probability of restoring the patient's cerebral blood flow after biological death has been confirmed [47]. In this regard, almost everywhere abroad, one or another method of isolating the abdominal perfusion region is used (in normothermic regional (abdominal) perfusion (NRP)) is used – balloon inflation in the aortic lumen above the diaphragm or application of a ligature on the aorta, after performing rapid laparotomy.

We did not use balloon insertion into the aortic lumen, because we consider the "inactivity" period of 20 minutes to be sufficient to ensure confirmation of irreversibility of cardiac arrest, if any, and to exclude the possibility of recovery of some part of the brain function. Exclusion of occluding aortic balloons from the protocols allows us to safely assume that in the nearest future, it will be possible to use heart and lungs from asystolic donors for clinical transplantation [48].

Despite repeated experiments on animals where the efficacy of thrombolytics was shown, as well as in our clinical experience of thrombolytics use (Streptokinase, Alteplase) in abdominal normothermic perfusion in situ, there are currently no reports on inclusion of this group of drugs in out-of-hospital donor protocols [6, 49, 50]. The same situation is observed with the use of mechanical and pharmacological leukoreduction in the donor body. Routine use of leukocyte filters has been described in isolated lung perfusion, where it has been shown that leukoreduction is associated with incidence of primary pulmonary graft dysfunction [51]. In our opinion, today these integral components of perfusion protocols are underestimated; they have significant potential to improve the functional status of organs obtained from asystolic donors to the moment of transplantation; in fact, without

their use, the donor therapeutic potential of ECMO is reduced to zero.

To summarize the discussion, it has to be said that out-of-hospital donors are a full-fledged donor resource, not only for kidney transplants, but also for such donor organs as liver, pancreas, lungs, when extracorporeal life support is used. In a recent European study evaluating the effectiveness of various post-mortem organ donation pathways in 2016, the use of out-of-hospital asystolic donors was 75%, compared with 91% of "controlled" asystolic donors and 93% of brain-dead donors [35]. Thus, over a 15-year period, 1,713 kidney transplants, 158 liver transplants, and 86 lung transplants from these donors were performed in Spain. These results were achieved with a rather high rejection rate (45% of kidneys and 62% of livers) mostly due to ineffective perfusion. At the same time, the actual one-year survival rate of kidney transplants was 87%, despite an increased rate of delayed graft function (78%) and early graft dysfunction (7%) compared with standard brain-dead donors. These results were later confirmed by several individual Spanish centers as well as by French and Italian studies [52].

CONCLUSION

Constant technologization of the medical industry leads to introduction of high-tech methods in the practice of critical care and life support medicine. The state of the art is the implementation of technologies for the use of mechanical cardiac compressing systems and ECMO in emergency medical care primarily in order to improve the efficiency and effectiveness of resuscitation measures. Possession of resuscitators and wide use of portable perfusion devices for ECMO, in combination with advanced resuscitation measures, can achieve survival of 5.92% of patients with sudden out-of-hospital circulatory arrest. In the case of ineffectiveness of life-saving measures, such medical technology allows switching over to the procedure for preserving the organs of a deceased donor and implementing the donor program in 16.47% of cases. The long-term outcomes of organ transplantation from asystolic donors, whose blood circulation was restored using ECMO, practically do not differ from the outcomes of transplantation from brain-dead donors. Thus, the across-the-board widespread technologization of resuscitation care, the use of perfusion technology and portable perfusion equipment as part of life support procedure, can potentially save the lives of patients with sudden out-of-hospital cardiac arrest and has the impressive potential to expand the pool of donor organs.

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