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COMPARATIVE STUDY OF LUNG PRECONDITIONING PROTOCOLS IN DONORS AFTER CIRCULATORY ARREST: AN EXPERIMENTAL RABBIT MODEL

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Objective: to perform a comparative analysis of donor lung preconditioning protocols in donors after circulatory arrest, followed by normothermic *ex vivo* lung perfusion (EVLP), using two approaches: topical lung cooling and continued artificial ventilation after circulatory arrest. **Materials and methods.** The study was conducted on male Grey Giant rabbits weighing 4.5–5.0 kg (n = 20). Group 1: Donor lung preconditioning after circulatory arrest using topical cooling (n = 10). Group 2: Donor lung preconditioning after circulatory arrest with continued artificial ventilation in protective modes (n = 10). To evaluate the viability and functional state of donor lungs following preconditioning and cold preservation, both groups underwent normothermic EVLP. Assessments included lactate concentration, perfusate gas composition, endoscopic evaluation of the tracheobronchial tree, and subsequent morphological examination. **Results.** After 60 minutes of cold preservation, all grafts demonstrated satisfactory gas exchange function during normothermic EVLP. In Group 1 (topical cooling), the oxygenation index (OI) at 60 minutes was 552 (461–599) and increased to 558 (462–603) at 120 minutes. In Group 2 (continuous artificial ventilation), OI was 358 (343–368) at 60 minutes, with a tendency to increase to 374 (349–395) at 120 minutes. The difference between the groups was statistically significant (p = 0.000). Lactate levels in both groups showed an upward trend, with a mean value of 6.99 ± 0.81, and no statistically significant intergroup differences were observed (p > 0.05). **Conclusion.** The study demonstrates the potential advantages of using topical cooling as part of the donor lung preconditioning protocol after cessation of effective circulation, employing a dextran-40-based preservation solution at all stages. This approach may increase the number of donor lungs suitable for transplantation.

Keywords: lung transplantation, normothermic ex vivo perfusion, organ donation, organ preservation, dextran-40.

INTRODUCTION

Donation after circulatory death (DCD) represents one of the most promising areas in modern transplantology, offering a viable solution to the persistent shortage of donor organs. Traditionally, lung transplantation has relied on donation after brain death (DBD); however, increasing attention is now being directed toward the use of lungs from DCD donors. This shift is driven by the growing need for donor lungs, improvements in organ preservation techniques, and the introduction of perfusion technologies.

In recent years, the use of lungs from DCD donors has increased markedly. According to 2018 data from the United States, lungs from DCD donors accounted for approximately 20% of all lung transplants. In Europe, this figure varies between countries, from 5% to 40%, yet overall shows a clear upward trend in the adoption of donors after circulatory death [1].

Clinical evidence indicates that outcomes of lung transplantation from DCD donors are comparable to those from DBD donors. International studies show that long-term recipient survival and graft function following DCD lung transplantation are not inferior to traditional lung transplants. Moreover, in some centers, DCD lungs constitute a substantial proportion of all transplanted organs, underscoring the effectiveness of this approach.

In the United States, the 1-year survival rate after lung transplantation from DCD donors is approximately 75–80%, which is slightly lower than the outcomes reported for DBD donors [2, 3]. In Europe, 1-year survival rates following DCD lung transplantation range from 65% to 90%, depending on the country, with results comparable to DBD transplantation observed in the Netherlands, Belgium, Spain, and Italy [3–5]. The 3-year survival rate after DCD lung transplantation is around 70%, which is close to the rates seen with DBD donors.

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However, DCD lung transplantation is associated with a higher incidence of primary graft dysfunction, largely due to ischemic injury resulting from the absence of lung perfusion after cardiac arrest. Unlike DBD donor lungs – where circulation is maintained until explantation – DCD lungs undergo a period of warm ischemia, which may impair graft quality [6].

Advances such as *ex vivo* lung perfusion (EVLP) have enabled functional assessment, recruitment, and more thorough perfusion of the pulmonary microvasculature prior to transplantation, thereby increasing the number of organs deemed suitable for transplantation [3, 7, 8].

This experimental study compares two protocols for lung explantation from DCD donors, followed by normothermic *ex vivo* perfusion. The first protocol involves topical cooling of the lungs in the pleural cavity using a preservative solution [9–11], while the second protocol utilizes continued mechanical ventilation after cardiac arrest [12, 13]. For both approaches, an original dextran-40–based solution was employed for lung preservation and perfusion [14, 15].

DESIGN OF THE EXPERIMENTAL WORK

The study was conducted on 20 male Grey Giant rabbits weighing 4.5–5.0 kg. All procedures complied with the requirements of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes and Directive 2010/63/EU. The animals were housed in laboratory cages under standardized conditions: controlled temperature (22 ± 2 °C), relative humidity (65%), a 12-hour light–dark cycle, regulated feeding, and ad libitum access to sterilized water. A two-week quarantine period was observed prior to experimentation. All procedures were reviewed and approved by the institutional Committee on Biological Safety and Bioethics.

The study was conducted in two experimental groups:

Group 1. DCD model with topical cooling of the donor lungs and without mechanical ventilation (MV). The lung graft was removed 40 minutes after circulatory arrest, followed by 6-hour cold storage preservation and 2-hour EVLP (N = 10).

Group 2. DCD model with continued MV. The lung graft was removed 40 minutes after circulatory arrest, followed by 6-hour cold storage preservation and 2-hour EVLP (N = 10).

After completing the EVLP procedure, a fragment of each graft was collected for histological examination.

MATERIALS AND METHODS

Donor lung procurement procedure

After preparing the donor animal according to aseptic and antiseptic standards, the surgical field was treated and isolated using sterile drapes. Surgical access was achieved via median sternotomy. Following hemostasis and mobilization of the major vessels, DCD was simulated. In Group 1, MV was continued, while in group 2, MV was discontinued and 50 ml of a dextran-40–based preservation solution was instilled into each pleural cavity, as shown in Fig. 1.

After a 30-minute exposure period, 30 ml of blood was withdrawn from the left ventricle, after which a cannula was inserted into the pulmonary artery. Antegrade perfusion with a dextran-40–based solution (OCS Lung Solution) cooled to 4 °C was initiated. A total of 60 ml of solution was administered using a syringe pump at a rate of 500 ml/hour with an exposure time of 7 minutes. This was followed by mobilization of the lungs. After mobilization, at the height of inspiration and below the distal tip of the endotracheal tube, the trachea was securely ligated and transected. The lungs were then immersed in the dextran-40–based solution at 4 °C and stored under cold preservation for 6 hours.

Anesthesia

Six hours prior to surgery, the donor animal was fasted. The rabbit was transported to the preoperative room for preparation, where sedation was initiated with Zoletil 100 (Virbac, France) 50 mg administered subcutaneously. Under aseptic conditions, an intravenous

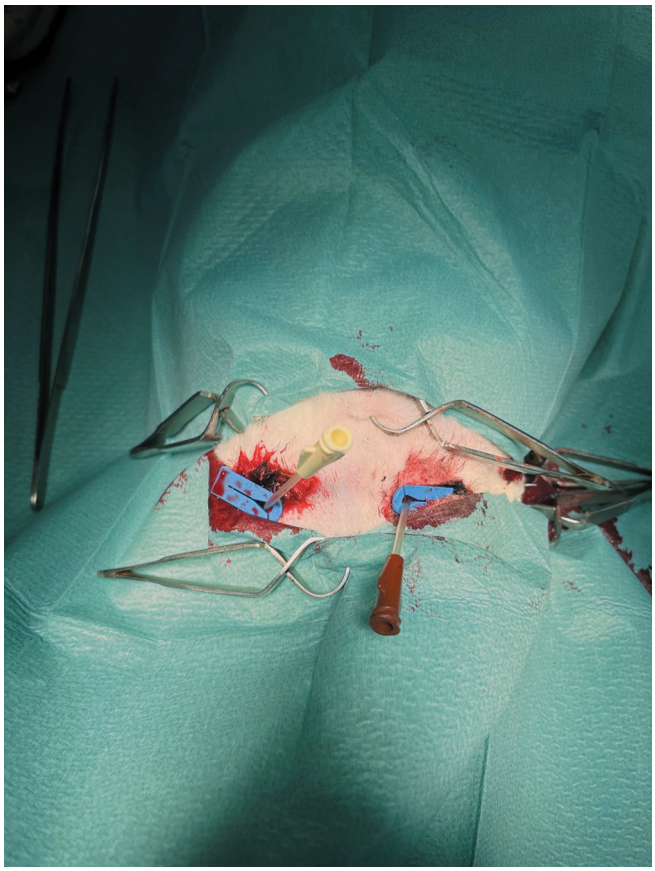

Fig. 1. Topical cooling of the lungs performed through drainage of the right and left pleural cavities using 8 Fr central venous catheters

catheter (Vasofix Certo 22G, BBraun, Germany) was inserted and secured. The animal was positioned in the supine position.

For anesthetic induction, atropine 0.3 mg and dexamethasone 2 mg were administered intravenously, followed by intravenous Zoletil 100 (Virbac, France) 50 mg and propofol (Fresenius Kabi, Germany) 25 mg. Direct laryngoscopy was performed, and tracheal intubation was carried out using a cuffed 3.5 cm endotracheal tube. After confirming correct tube placement, rocuronium (Fresenius Kabi, Germany) 10 mg was administered.

MV was initiated using a WATO EX-65 Pro Vet ventilator (Mindray, China) in VCV mode with the following parameters: tidal volume 50 ml, respiratory rate 35/min, Ppeak 17 cm H_2O, PEEP 3 cm H_2O, I:E ratio 1:1, FiO_2 0.6, and $EtCO_2$ 40 mmHg.

Physiological monitoring was performed using an ePM 12M Vet monitor (Mindray, China). Average values included HR 170/min, SpO_2 98%, and noninvasive arterial pressure of 90/45 mmHg.

Analgesia was maintained with intravenous tramadol (Tramvet, Russia) 25 mg, and sedation was supported with isoflurane (Baxter, USA) at a concentration of 1.5%. Hemodynamic stability was achieved with continuous intravenous infusion of Panangin (Gedeon Richter, Hungary) at 10 ml/hour and norepinephrine at 100 ng/kg.

Prior to inducing circulatory arrest to simulate DCD, heparin 10,000 IU and Vasaprostane (IDT BIOLOGIKA, Germany) 10 µg were administered intravenously. Circulatory arrest was induced using a 20 J electric shock delivered by an electrical fibrillator. An exposure period of 30 minutes followed.

During the exposure, all drug infusions were discontinued. Ventilation parameters were changed: In group 1, MV was discontinued, while in group 2, MV was continued with modified parameters – tidal volume 30 ml, respiratory rate 15/min, Ppeak 10 cm H_2O, PEEP 5 cm H_2O, I:E 1:1, and FiO_2 1.0.

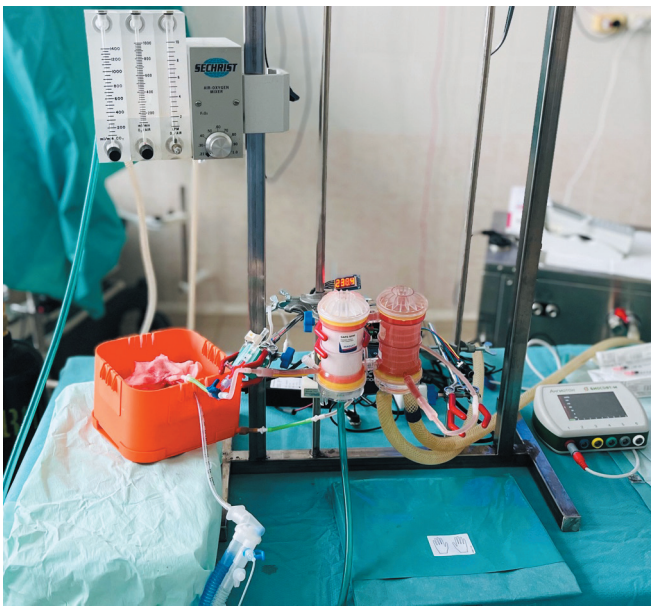

Fig. 2. Perfusion circuit setup for normothermic EVLP

After the 30-minute exposure period, a recruitment maneuver was performed, and the lung procurement procedure was initiated, followed by cold storage preservation.

Ex vivo perfusion procedure

To initiate normothermic perfusion of donor lungs, the stroke volume (SV) of the donor's left ventricle was measured using a GE Logiq V2 ultrasound system in M-mode and Doppler echocardiography with the animal positioned in the right lateral decubitus position. The average SV obtained was 2.6 ml. Cardiac output (CO) was subsequently calculated using the formula CO = SV × HR, where HR is the heart rate. The mean cardiac output was 410 ml/min.

For EVLP using 3D modeling techniques, an organ container was fabricated on a Picaso Designer X Pro 3D printer. This biocompatible plastic reservoir functioned both as a cardiotomy chamber and as a platform for securing the donor lungs during perfusion. The container was reusable and was gas sterilized in individual packaging after each procedure.

The extracorporeal circuit included a reservoir for positioning the donor lungs, a roller pump, a heat exchanger, a laboratory oxygenator with a low priming volume, a flow sensor, and a pressure sensor.

All components were assembled under strict aseptic and antiseptic conditions (Fig. 2). The circuit was primed with 20 ml of a dextran-40–based solution (OCS Lung Solution). Through a leukocyte-depleting infusion filter, 25 ml of whole donor blood was added. The perfusate was supplemented with the following: methylprednisolone 50 mg, vasoprostane – 25 mcg, heparin – 1000 mg, calcium chloride 10% – 1 ml, insulin P – 3 units, magnesium sulfate 25% – 0.2 ml, and ceftriaxone – 100 mg. The total perfusate volume was 50 ml. Prior to initiating lung perfusion, the solution was heated to 28 °C and circulated at a rate of 50 ml/min.

After 6 hours of cold storage preservation, surgical preparation of the lung grafts was initiated in both groups. A 2.2–2.4 mm cannula was inserted into the pulmonary artery, and a 3.0-mm uncuffed endotracheal tube was placed into the trachea. The left atrium was opened to ensure unobstructed perfusate outflow. The heart–lung bloc was then positioned inside the perfusion chamber. The pulmonary vascular bed was filled retrogradely, with careful monitoring to maintain the filling pressure below 3 mmHg. Following vascular filling and deaeration, the perfusion line was connected to the pulmonary artery cannula using an airless technique. Bronchoscopy of the lung graft was subsequently performed using an Ambu aScope™ 4 Broncho Slim 3.8/1.2 disposable broncho-

scope. The obtained endoscopic view is presented in Fig. 3.

The EVLP procedure was conducted in accordance with the Lund protocol. The initial perfusion rate was set at 100 ml/min (25–30% of CO), with pulmonary artery pressure maintained below 25 mmHg and perfusate temperature at 28 °C. Warming of the graft and gradual achievement of the target perfusion parameters required 30 minutes. A general view of the donor lungs during normothermic perfusion is shown in Fig. 4.

Artificial lung ventilation was initiated at a perfusate temperature of 34 °C, 15 minutes after the start of EVLP. Initial ventilation parameters were: tidal volume 2–4 ml/kg of donor body weight, respiratory rate 10/min, Ppeak 20 cm H_2O, PEEP 5 cm H_2O, I:E 1:1, and FiO_2 0.21. The target perfusion parameters were a flow rate of 410–420 ml/min (100% of CO), pulmonary artery pressure up to 25 mmHg, and perfusate temperature of 38.5 °C. Target ventilation parameters included tidal volume 6 ml/kg, respiratory rate 17/min, Ppeak 25 cm H_2O, PEEP 5 cm H_2O, I:E 1:1, and FiO_2 0.21. The EVLP procedure lasted for 120 minutes.

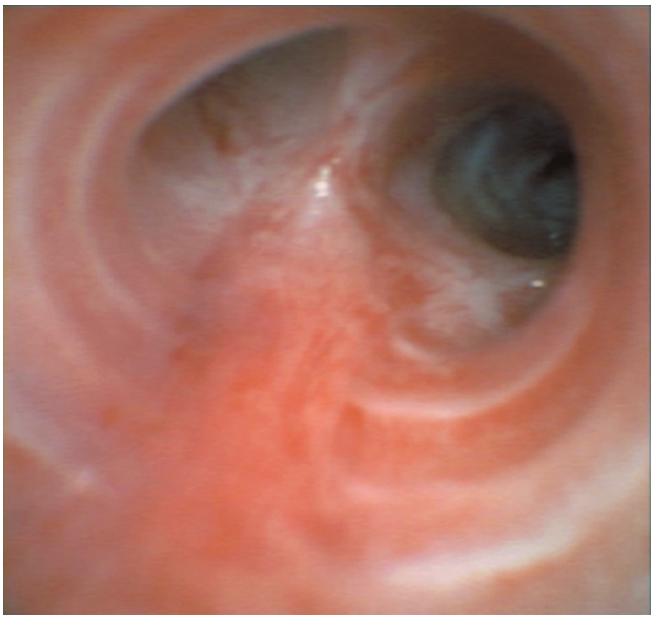

Fig. 3. Endoscopic image during normothermic perfusion

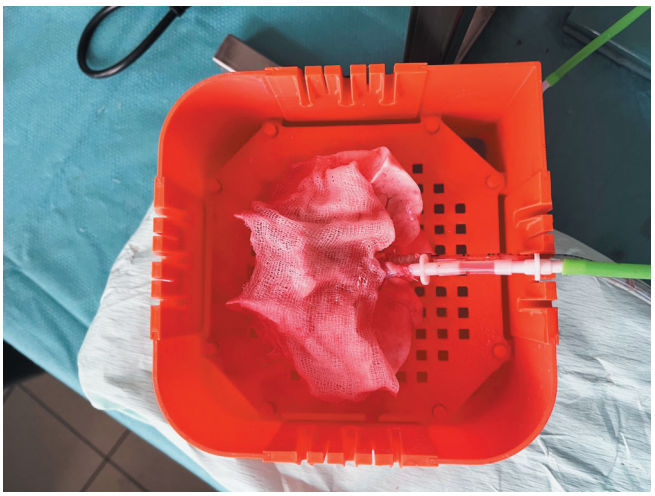

Fig. 4. Lung graft placed in the perfusion reservoir. The pulmonary artery trunk is cannulated, and the trachea is intubated for ventilation

During normothermic perfusion, a base gas mixture of 21% O_2, 5% CO_2, and 74% N_2 was supplied through the oxygenator. Every 30 minutes, the functional status of the donor lungs was assessed, and a deoxygenating mixture consisting of 5% CO_2 and 95% N_2 was administered.

At the end of EVLP, the donor lungs were preserved using 60 ml of a dextran-40–based solution (OCS Lung Solution), infused through the pulmonary artery cannula at a rate of 500 ml/hour. Lung parenchyma samples were then placed in 10% formalin for histological analysis.

Statistical analysis was performed using StatTech v.3.1.10 software (StatTech LLC, Russia). Quantitative variables were tested for normality using the Shapiro–Wilk test (sample size <50). Variables with a normal distribution were summarized as mean (M) and standard deviation (SD), with corresponding 95% confidence intervals (95% CI).

For comparisons of three or more related groups on normally distributed quantitative variables, a one-way repeated-measures analysis of variance (ANOVA) was applied. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Assessment of the functional status of donor lungs during normothermic perfusion

Despite the extensive list of recorded indicators and biochemical analysis results, the oxygenation index (PaO_2/FiO_2) served as the principal criterion for evaluating the gas exchange capacity of the lungs. This calculated ratio reflects the efficiency of oxygen transfer into the pulmonary venous blood relative to the fraction of inspired oxygen. As such, it is considered a key indicator of ischemia–reperfusion injury severity and the preservation of adequate alveolar blood flow. The dynamics of changes in the oxygenation index (OI) in the two experimental groups – used to compare the effectiveness of donor lung preconditioning protocols during normothermic *ex vivo* perfusion – are presented in shown Fig. 5.

Thus, by 60 minutes after initiation of transplant revitalization on the extracorporeal circuit, both groups reached the OI threshold level of approximately 350. However, group 1 showed significantly higher OI values – 552 (461–599) compared with 358 (343–368) in group 2. This difference reflects the more pronounced ischemia–reperfusion injury observed in group 2 during donor lung preconditioning at the DCD stage and subsequent cold storage.

After 120 minutes of EVLP, both groups showed a moderate decline in OI compared with their peaks at 90 minutes – 594 (500–619) in group 1 and 408 (396–418) in group 2 – consistent with the expected increase in interstitial edema. By the end of the 120-minute EVLP period, mean OI remained significantly higher in Group 1 at 558 (462–603) compared with 374 (349–395) in Group 2.

Overall, these results demonstrate the superior effectiveness of topical cooling during DCD lung preconditioning compared with continued protective MV, with statistical significance confirmed at $p = 0.000$.

Lactate levels, assessed as a biochemical marker of ischemia–reperfusion injury, showed a steady increase throughout the perfusion period due to the absence of metabolic clearance mechanisms in the *ex vivo* circuit (Fig. 6).

Baseline lactate levels were recorded 60 minutes after the start of perfusion in both groups, as earlier measurements are not informative for assessing initial reperfusion injury. In group 1, mean lactate level was 0.7 ± 0.6 mmol/L, while in group 2 it was 1.54 ± 0.58 mmol/L. No statistically significant differences were found between the groups at this initial time point ($p > 0.05$), indicating that the two DCD preconditioning protocols did not differ in terms of severity of primary ischemia–reperfusion injury.

Throughout the perfusion period, both groups showed a clear and progressive increase in lactate levels. By the final measurement at 120 minutes, mean lactate levels reached 6.44 ± 1.35 mmol/L in group 1 and 7.02 ± 1.55 mmol/L in group 2. These values remained below the critical threshold of 12 mmol/L. At all time points, intergroup differences remained statistically insignificant ($p > 0.05$). Thus, lactate level did not prove to be a reliable comparative marker for assessing the effectiveness of donor lung preconditioning protocols in the DCD model. The most informative indicators were those reflecting the functional status of the grafts.

Assessment of histological changes in donor lungs

Histological evaluation of lung micro-preparations after preconditioning in the two comparative groups and subsequent EVLP was essential to verify the efficacy and safety of the protocols. Microstructural analysis provided reliable evidence of ischemia-reperfusion injury, its severity, and potential reversibility. In group 1, minimal pathomorphological changes were observed in the lung parenchyma at the final stage of the study (Fig. 7).

Across all samples, the parenchyma exhibited histological signs of functional tissue without significant pathological alterations. Most sections showed well-inflated alveoli, with microatelectatic areas being sparse and unevenly distributed. Moderate interstitial infiltration was present in a few samples. No notable differences in microstructure were observed within group 1 samples: interalveolar septa remained thin, bronchial walls displayed normal histology, and vascular blood filling was moderate.

In group 2, which underwent the artificial ventilation preconditioning protocol, primary graft dysfunction was observed after 120 minutes of EVLP. This corresponded with the reduced OI recorded during functional assess-

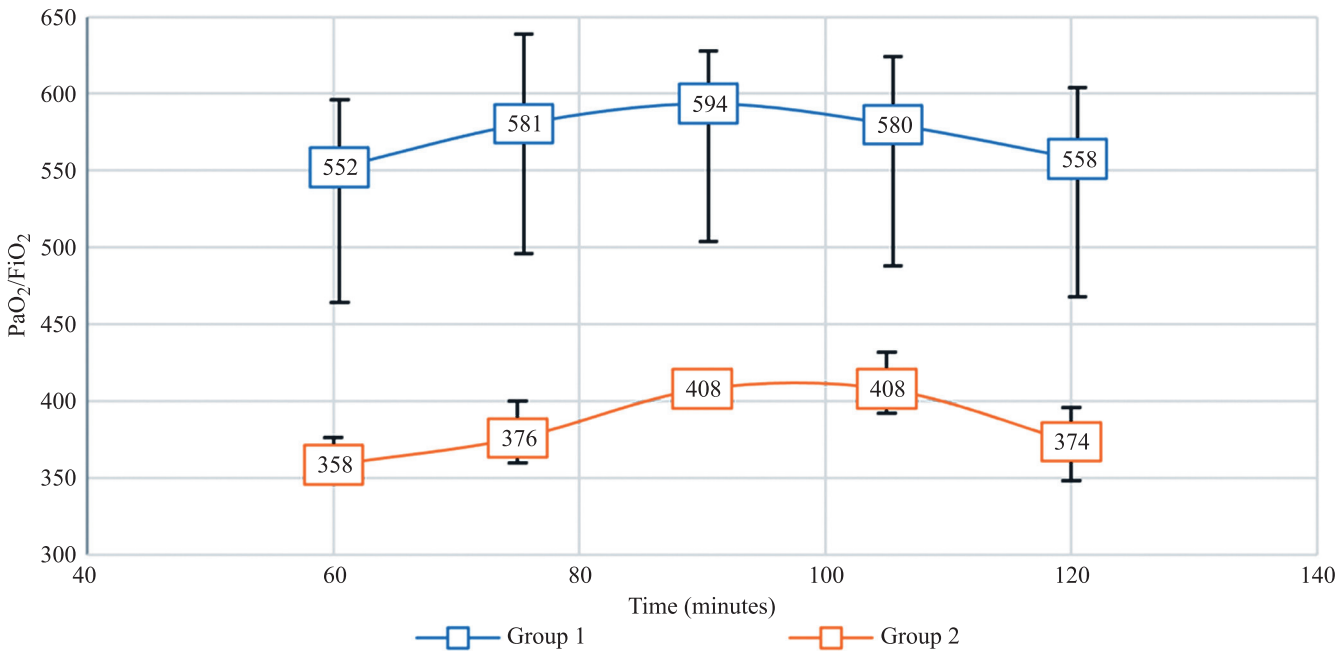

Fig. 5. Dynamics of changes in the PaO_2/FiO_2 ratio. The graph illustrates the mean oxygenation index (PaO_2/FiO_2) during normothermic EVLP. Values are presented as mean, minimum, and maximum. Measurements were taken at 60, 75, 90, 105, and 120 minutes

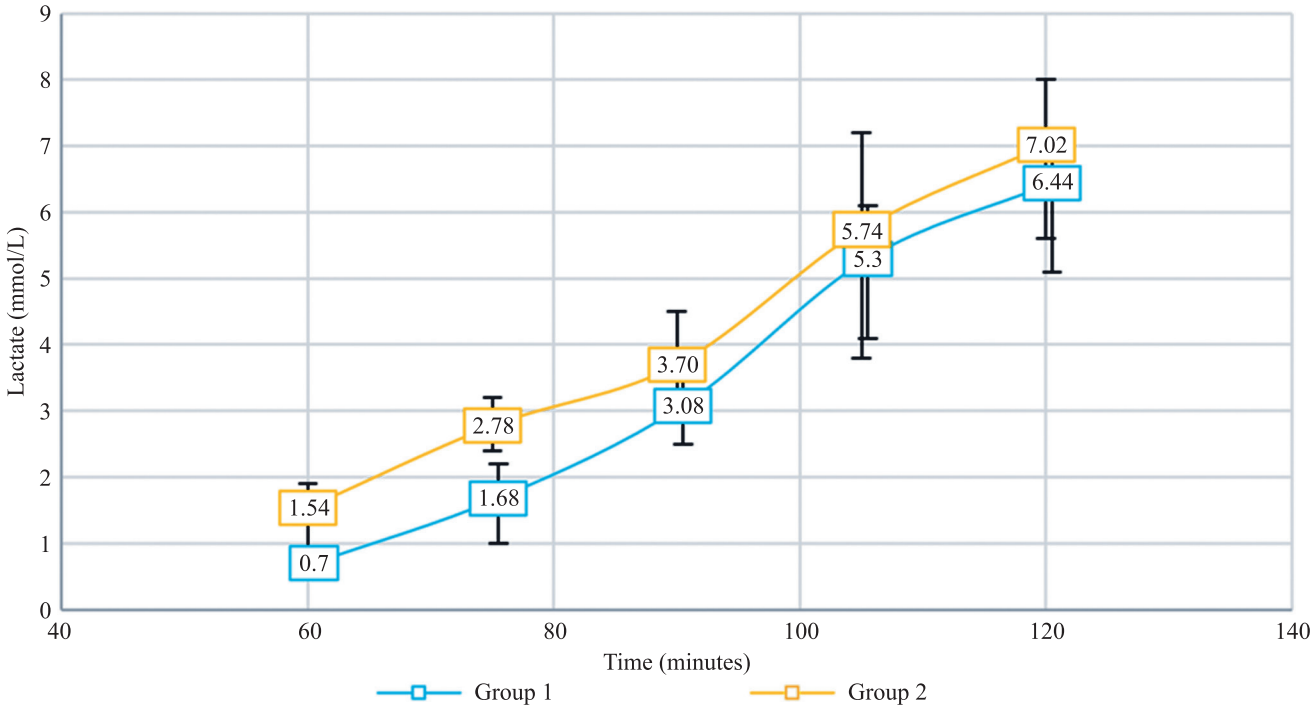

Fig. 6. Dynamics of lactate levels during *ex vivo* perfusion. The graph presents the mean lactate levels measured during normothermic EVLP. Values are shown as mean, minimum, and maximum. Measurements were taken at 60, 75, 90, 105, and 120 minutes

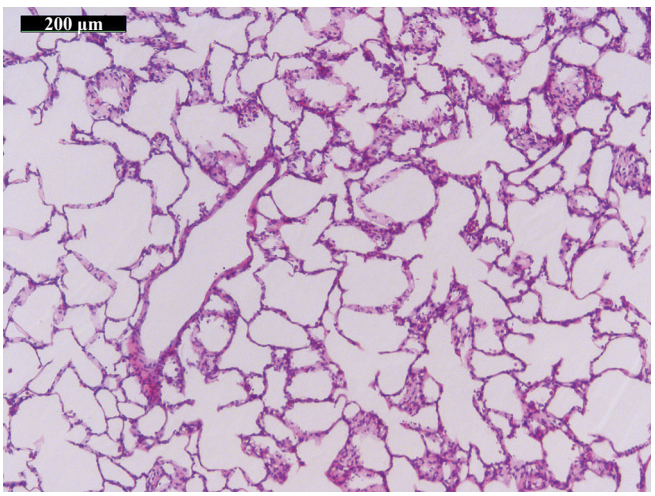

Fig. 7. Histological image of donor lung parenchyma after normothermic EVLP in Group 1 (Spanish protocol). Magnification: 200 µm

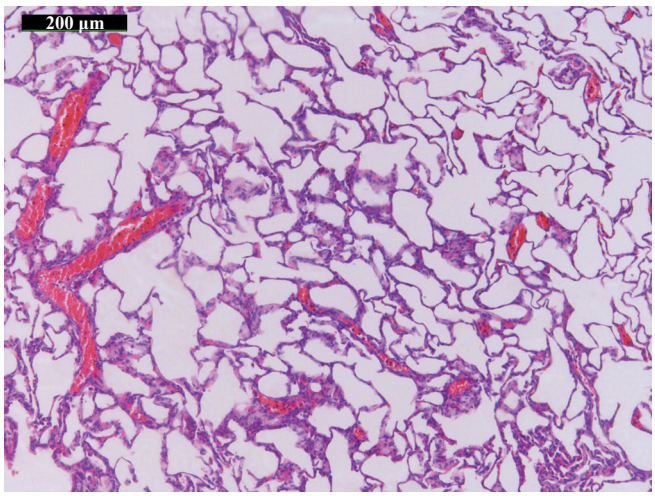

Fig. 8. Histological image of donor lung parenchyma after normothermic EVLP in Group 2 (Italian protocol). Magnification: ×200

ment of the graft. Histological changes were characterized by moderate interstitial edema in the parenchyma and subendothelial edema in the perivascular spaces (Fig. 8).

At 200 µm magnification, lung micro-preparations from group 2 showed fragments of parenchyma with pronounced hyperemia in both macro- and microcirculatory vessels, areas of dystelectasis, intra-alveolar hemorrhages, and desquamation of pneumocytes. Particular importance was attached to the classic signs of dysfunction associated with ischemia-reperfusion injury – edema of the interalveolar septa accompanied by mixed inflammatory infiltration of the interstitium.

DISCUSSION

Data from this experimental study enabled a comparative assessment of two donor lung procurement protocols in DCD donors – topical cooling versus continued MV after cardiac arrest. EVLP outcomes indicate that the topical cooling technique provides more stable gas exchange and metabolic activity of the transplant. Specifically, the OI in group 1 (topical cooling) was consistently

higher at all observation time points compared to group 2 (continued MV), suggesting better preservation of the alveolar-capillary membrane and reduced severity of ischemic injury. Lactate levels in group 1 remained lower, reflecting more efficient tissue metabolism and reduced accumulation of anaerobic glycolysis products. This likely results from faster and more uniform warm protection of the lung parenchyma achieved through topical cooling, whereas continued ventilation after cardiac arrest may offer insufficient protection against reperfusion injury and, in some cases, exacerbate alveolar edema, as confirmed endoscopically in two observations in group 2. Notably, both protocols employed the same dextran-40-based preservative solution, minimizing variability due associated with composition of the perfusate and allowing us to focus on the differences between the procurement methods.

The presented data suggest that the lung procurement technique using topical cooling provides a more pronounced protective effect in the DCD model compared to continuous MV. This finding aligns with previous clinical and experimental studies emphasizing the importance of rapid initiation of cooling and minimization of reperfusion stress as key factors for successful preservation of lungs from DCD donors [16, 17]. Limitations of the present study include the small sample size and the use of a surrogate animal model (rabbits), which warrants caution when extrapolating these results to clinical practice. Nevertheless, the findings provide a solid foundation for further research and optimization of protocols for conditioning lungs from DCD donors.

CONCLUSION

This experimental study confirmed the feasibility of lung donation after cardiac arrest with normothermic normothermic EVLP using an original dextran-40-based preservation and perfusion solution. The use of this solution allowed donor lungs to be preserved without significant alveolar edema in most cases and maintained satisfactory gas exchange function during perfusion. The results indicate that lung procurement with topical cooling provides more effective organ preservation, as reflected by superior oxygenation and metabolic indicators during perfusion. Consistent with published experimental and clinical studies, the clinical implementation of lung donation after circulatory death has the potential to increase the donor pool without substantially raising the risk of primary graft dysfunction, while maintaining long-term survival rates comparable to those observed with lungs from brain-dead donors.

The authors declare no conflict of interest.

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