Prolonged venoarterial extracorporeal membrane oxygenation after transplantation restores functional integrity of severely injured lung allografts and prevents the development of pulmonary graft failure in a pig model

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Objective: Prolonged venoarterial extracorporeal membrane oxygenation support during transplantation provides reduction of pulmonary artery flow and allows for protective ventilation. This approach might have the potential to restore function of lungs that would be unsuitable for transplantation.

Methods: Left lung transplantation was performed on 16 pigs. Lungs from brain-dead animals were stored for 22 hours at 4°C. Recipients in group A (n = 8) underwent transplantation without cardiopulmonary support followed by ventilation with 10 mL/kg body weight tidal volume. Animals in group B (n = 8) underwent transplantation during venoarterial extracorporeal membrane oxygenation, which was continued for 22 hours, and received low-tidal-volume (5 mL/kg body weight) ventilation. One hour after transplantation, the right lung was excluded. Graft function was compared immediately after exclusion of the contralateral lung (time point 1), 1 hour later (time point 2), and 1 hour after discontinuation of extracorporeal membrane oxygenation (time point 3).

Results: Four animals in group A did not reach time point 2; all died of pulmonary edema. All animals in group B survived, and at time point 3, the mean Pa_{O_2} value was 323 ± 129 mm Hg. At time point 2, oxygenation and lung compliance were higher in group B than in group A, whereas pulmonary artery pressure was lower. The same was true when comparing results of group B at time point 3 with results of group A at time point 2.

Conclusions: Transplantation during extracorporeal membrane oxygenation with continued use for 24 hours restores function of damaged donor lungs. This could expand the donor pool through wider use of marginal donors.

According to the report of the International Society for Heart and Lung Transplantation, primary pulmonary graft failure (PGF) accounts for almost one third of early deaths.[1] PGF is a result of repetitive traumatic episodes involving the allograft. Main contributors are brain death, preservation and storage conditions, and the effects of reperfusion.[2]

PGF usually presents with the clinical picture of severe reperfusion edema. Once edema is established, the standard course of treatment is aggressive ventilation with high pressure patterns together with intravenous inotropic support. However, this course of treatment itself causes further damage to the lung because of overinflation and a further increase in pulmonary artery pressure (PAP).

The importance of controlled low-pressure perfusion, as well as protective low-tidal-volume ventilation, for recovery of injured lungs has been demonstrated in several clinical and experimental reports.[3-7] In lung transplantation both controlled low-pressure perfusion and low-tidal-volume ventilation can be provided by venoarterial extracorporeal membrane oxygenation (ECMO). Usually, ECMO is applied for the treatment of already established graft failure.[8,9] However, it can also be used intraoperatively as an alternative to cardiopulmonary bypass (CPB) and then be prolonged into the postoperative period to provide optimal reperfusion conditions to the transplanted allograft.[10] In our clinical experience with this approach, we have seen excellent initial graft function, even with very marginal donor organs.

The aim of the study was to investigate the effect of intraoperative and prolonged postoperative ECMO support on the early allograft function of critically injured donor lungs in a standardized experimental transplantation setting.

MATERIALS AND METHODS

The study was performed in accordance with the Austrian Animal Research Statute (1988) and was approved by the local ethics committee of the Medical Faculty, University of Vienna, Vienna, Austria. Furthermore, the study was conducted in compliance with the principles of laboratory animal care formulated by the National Society for Medical Research and the ''Guide for the care and use of laboratory animals,'' prepared by the

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Abbreviations and Acronyms

ARDS = acute respiratory distress syndrome
BW = body weight
CO = cardiac output
CPB = cardiopulmonary bypass
ECMO = extracorporeal membrane oxygenation
F_{IO_2} = fraction of inspired oxygen
PAP = pulmonary artery pressure
PGF = pulmonary graft failure

National Institutes of Health (National Institutes of Health publication no. 96-03, revised 1996).

Experimental Groups

Thirty-two healthy pigs (German large white pigs) were used. Sixteen served as brain-dead donors, and 16 served as recipients. Four hours after induction of brain death, the donor lungs were harvested and stored for a cold ischemic period of 22 hours. The transplantation procedure was a left single lung transplantation followed by crossclamping of the right lung 1 hour after reperfusion.

The 16 recipient pigs were divided into 2 groups. Group A consisted of 8 pigs undergoing transplantation without ECMO support with standard postoperative ventilation at 10 mL/kg body weight (BW). Group B consisted of 8 pigs undergoing transplantation with intraoperative and postoperative (22 hours) ECMO support receiving protective low-tidal-volume postoperative ventilation at 5 mL/kg BW.

Functional assessment was performed 10 minutes after exclusion of the contralateral right lung (time point 1), 1 hour later (time point 2), and 22 hours later in group B (ie, 1 hour after weaning from ECMO; time point 3). Graft function was compared between the groups by measuring oxygenation, PAP, dynamic lung compliance, and extravascular lung water content (wet/dry weight ratio).

Donor Procedure

Anesthesia. An arterial line for invasive pressure monitoring (Smiths Medical, Kirchseeon, Germany) was placed in the right internal carotid artery. A venous line for drugs and fluid replacement was placed in the internal jugular vein. For introduction of a Swan–Ganz catheter (size 7.5F, Vigilance; Edward Lifesciences, Irvine, Calif), the external jugular vein was used. Urine output was monitored through a balloon catheter introduced through a suprasymphyseal lower median laparotomy. Premedication consisted of 20 mg/kg ketamine (Ketavet; Pharmacia–Upjohn, Uppsala, Sweden) plus 1.76 mg/kg acepromazine (Vanastress; Vana, Vienna, Austria) administered intramuscularly. Anesthesia was introduced with 15 mg/kg thiopental, 15 mg of piritramid (Dipidolor; Janssen-Cilag Pharma, Wien, Austria), and 20 mg of rocuronium bromide (Esmeron; Organon, Oss, The Netherlands) administered intravenously and maintained with 0.1 mg $\cdot$ kg^{-1} $\cdot$ h^{-1} piritramid, 10 mg $\cdot$ kg^{-1} $\cdot$ h^{-1} propofol (Propofol Fresenius 2%; Fresenius Kabi, Linz, Austria), and 0.1 mg $\cdot$ kg^{-1} $\cdot$ h^{-1} rocuronium bromide administered intravenously for muscle relaxation. All animals were fully heparinized with 300 IU/kg BW Na-Heparin (Heparin Immuno; EBEWE Pharma, Unterach Austria) administered intravenously before cross clamping of the aorta. Animals were intubated with endotracheal tube Ch 8 (Rüsch, Kernen, Germany) and a ventilator (Dräger Primus; Dräger, Luebeck, Germany), and settings were as follows: tidal volume, 10 mL/kg BW; frequency, 20/min; fraction of inspired oxygen (F_{IO_2}), 0.5 to 1.0; inspiratory/expiratory time ratio, 1:2; positive end-expiratory pressure, 5 cm H_2O; and end-tidal CO_2 target value, 40 mm Hg.

Brain death procedure. After induction and maintenance of anesthesia, animals were placed in a ventral decubitus position. A balloon catheter was placed over the dura mater and pushed into the extradural space. Gradual balloon inflation with 25 mL of fluid (10+5+5 mL/10 minutes and 5 mL after a further 30 minutes) caused brain death. Lungs were harvested 4 hours later.

Lung harvesting. In contrast to the clinical routine, donor animals did not receive steroid medication to avoid any possible effect on pathways of the brain death–induced lung injury. The brain-dead pig was placed in the dorsal position, and a longitudinal sternotomy was performed. An inflow catheter was placed in the pulmonary artery through a purse-string suture on the right ventricular outflow tract. Both caval veins, together with the ascending aorta, were crossclamped, and the left auricular appendix was incised to provide drainage. The lungs were then perfused with an antegrade flush of 50 mL/kg cold low potassium dextran solution (Perfadex; Vitrolife, Gothenburg, Sweden) supplemented with 0.3 mL/L Tris buffer. Then an ice slush was placed in both pleural cavities and the mediastinum. During this period, the lungs were ventilated with 50% oxygen. En bloc harvesting of the heart and lungs together with the esophagus was performed, and before closure of the trachea with a stapler, the donor lungs were moderately inflated. Organs were then wrapped in gauze, placed in an insulated ice bag filled with low potassium dextran solution, and stored at 4°C for 22 hours.

Recipient Procedure

Anesthesia. Anesthesia for the recipient animals was identical as for the donor pigs. One single dose of 5000 IU Na-Heparin and 500 mg of imipenem (Tienam; Merck Sharp & Dohme, Haarlem, The Netherlands) was administered intravenously. Immunosuppression consisted of a single intravenous dose of 500 mg of methylprednisolone (Solu-Medrol, Pharmacia–Upjohn) administered immediately before reperfusion.

Implantation. The donor lung was then reimplanted with 4-0 polydioxanone running sutures for the bronchial anastomosis and 5-0 Prolene sutures for the pulmonary artery and left atrium. The implanted lung underwent retrograde and antegrade deairing and flushing according to standard procedures. Thereafter, the arterial clamp was partially released for 10 minutes to provide controlled reperfusion. One hour later, the bronchus and artery of the contralateral right lung were crossclamped. Ventilation to the transplanted lung was begun during reperfusion by using the standard method in group A and by using low tidal volumes in group B. At the end of the experiments, animals were killed by clamping of the left pulmonary artery.

ECMO management. For the animals in group B, the Medtronic Biomedicus portable bypass system with a hollow-fiber oxygenator (Medtronic CPMPCB Affinity BPX-80; Medtronic, Minneapolis, Minn) and an integrated heat exchanger was used for ECMO support. After thoracotomy, direct central cannulation of the ascending aorta (Medtronic DLP 22F Curved Tip) and the inferior caval vein (Medtronic DLP 32F Single Stage) was performed. Both the cannulae and the circuit were heparin coated (Medtronic Carmeda BioActive Surface). Priming solution was 200 mL of Ringer's Lactate solution. The flow was set at 50% of initial cardiac output (CO). This support was maintained throughout the whole transplantation procedure and continued for a further 22 hours. Thereafter, the pig was gradually weaned from ECMO. One hour later, the final functional assessment (time point 3) was performed.

Assessments

All arterial blood gas samples were taken from the right internal carotid artery after a test ventilation period of at least 10 minutes at an F_{IO_2} of 1.0 (ABL800 Flex Radiometer, Copenhagen, Denmark). Heart rate, arterial blood pressure, oxygen saturation, central venous pressure, and PAP were continuously monitored (PPG Hellige, Freiburg, Germany). Dynamic compliance was measured with a volume-controlled ventilator (Dräger Primus; Drägerwerk, Luebeck, Germany). Lung biopsy samples were taken from the anterior margin of the lower lobe.