CARDIOTHORACIC TRANSPLANTATION

LOW-POTASSIUM DEXTRAN SOLUTION AMELIORATES REPERFUSION INJURY OF THE LUNG AND PROTECTS SURFACTANT FUNCTION

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Objective: This study was designed to compare the effect of lung preservation with low-potassium dextran solution and Euro-Collins solution on reperfusion injury and surfactant function by using an in situ model of warm ischemia.

Methods: The left lungs of 6 minipigs were selectively perfused with Euro-Collins solution. In an additional 6 animals low-potassium dextran solution was used for flush perfusion. After 90 minutes of warm ischemia, the lungs were reperfused, and the contralateral pulmonary artery and bronchus were clamped. Hemodynamic and respiratory measurements were obtained for 7 hours of reperfusion. Surface tension of bronchoalveolar lavage and surfactant small and large aggregates were determined before perfusion (right lung) and after 2 hours of reperfusion (left lung).

Results: In the group receiving Euro-Collins solution, right heart failure developed within 215 ± 39 minutes of reperfusion. An increase in minimal surface tension ($P = .03$), surfactant small aggregates/large aggregates ratio ($P = .003$), and bronchoalveolar lavage protein content ($P = .012$) were found after 2 hours of reperfusion. In the group receiving low-potassium dextran solution, all minipigs survived ($P = .0001$). Dynamic lung compliance ($P = .034$) and oxygen tension/inspired oxygen fraction ratios were higher ($P = .0001$). Lung water content was lower ($P = .049$). The increase of minimal surface tension ($P = .02$) and bronchoalveolar lavage protein concentration ($P = .015$) were significantly less.

Conclusion: Preservation of the lung with Euro-Collins solution leads to a reduction of physical surfactant function during reperfusion. Low-potassium dextran solution protects surfactant function and metabolism, thereby reducing reperfusion injury of the lung. (J Thorac Cardiovasc Surg 2000;120:566-72)

Pulmonary allograft reperfusion injury remains a significant and common problem in clinical lung transplantation. Perioperative mortality still is in the range of 10% to 15%, and reperfusion injury is one of the most frequent causes of early death.¹ The incidence of reperfusion injury has been reported to range from 20% to 40% in different lung transplant programs.² Clinical

symptoms range from mild reduction of compliance of the lung to failure of the graft. The requirement of extracorporeal support was reported in 7.4% of 215 recipients after lung transplantation.³ Numerous studies have been undertaken to elucidate the pathophysiology and to improve function of the reperfused graft. One of the findings is the importance of endothelial and alveo-

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lar type II cell integrity after transplantation.⁴ It has been shown earlier that flush perfusion of the lung with Euro-Collins (EC) solution, which still is the most common preservation technique, leads to impairment of endothelial function.⁵ However, low-potassium dextran (LPD) solution was found to be superior to EC solution regarding preservation of endothelial function.⁶ In addition, a comparison of an extracellular preservation solution, such as LPD solution, with the currently used solution of intracellular ion composition (EC solution) revealed less cytotoxicity and improved metabolic activity of type II pneumocytes after preservation with LPD solution.⁷ In lungs preserved with EC solution, reduction of surfactant activity was found in experimental lung transplantation.⁸ Supplementation with surfactant preparations has improved graft function in the reperfusion period after experimental⁹ and, in isolated cases, clinical lung transplantation.¹⁰

This study was designed to compare lung function, surfactant activity, and metabolism after preservation either with EC or LPD solution during a reperfusion period.

Methods

Experimental groups. To compare the effect of 2 different preservation solutions, 12 minipigs were randomized into 2 groups of 6 animals each. In the first group, preservation was performed with EC solution, and in the second group, LPD solution was used.

Surgical preparation. Female minipigs (22-30 kg) were anesthetized with sodium pentobarbital (10 mg/kg) and fentanyl (1 µg/kg), followed by fentanyl infusion at a rate of 1 µg · kg⁻¹ · h⁻¹. The animals were intubated and ventilated with 50% oxygen (inspiratory/expiratory ratio, 1:1; positive end-expiratory pressure, 5 mm Hg) in a pressure-controlled mode (ventilatory cycles, 10/min; maximum inspiratory pressure, 20 mm Hg). A Swan-Ganz catheter (7.5F; Baxter Healthcare Corporation, Irvine, Calif) and a catheter to monitor arterial pressure were placed into the right carotid artery and internal jugular vein, respectively. A left thoracotomy in the fifth intercostal space was performed. The pericardium was opened. A catheter for measurement of pressure was placed into the left atrium. The left pulmonary artery, as well as the tracheal bifurcation and the pulmonary veins, were dissected. Umbilical tapes were applied to the right and left pulmonary arteries and the right main bronchus. Heparin (3 mg/kg) was administered intravenously. A catheter to infuse preservation solution was inserted through the main pulmonary artery into the left main pulmonary artery and stabilized there by tightening of the umbilical tape. A clamp was placed onto the left atrium so as to close the left pulmonary veins. The upper and lower pulmonary veins were incised. Ventilation was continued, and cold (4°C) preservation solution was then infused into the left pulmonary artery. The left lung was flushed for 3

to 5 minutes for a total volume of 40 mL/kg. Thereafter, the incisions of the pulmonary veins were closed with running 5-0 Prolene sutures (Ethicon, Inc, Somerville, NJ). No interval of cold storage of the left lung was used. After a warm ischemic time of 90 minutes, the clamps were taken off the left atrium. The perfusion cannulas were removed so that reperfusion of the left lung was initiated. After 10 minutes of reperfusion, the right pulmonary artery was clamped, as was the main right bronchus. Both umbilical tapes were tied. During the reperfusion period, the chest was temporarily closed, and external warming was applied to maintain body and left lung temperatures of 36.0°C to 37.0°C. Inotropic support to mitigate the effects of right heart insufficiency was administered (adrenaline infusion up to 0.5 µg · kg⁻¹ · min⁻¹) when systolic arterial pressure decreased below 60 mm Hg. Experiments were terminated by means of a pentobarbital overdose after 7 hours of reperfusion or when systolic arterial pressure fell below 40 mm Hg despite inotropic support. Thereafter, a large specimen of the left lower lobe was taken for measurement of lung water content.

Measurements of lung function. In all experiments, atrial as well as systemic (carotid) arterial and pulmonary arterial pressures were recorded online. Dynamic lung compliance ($C = V_t / [P_{\text{eip}} - P_{\text{exp}}]$, where V_t = tidal volume, P_{eip} = positive end-inspiratory pressure, and P_{exp} = positive end-expiratory pressure) was monitored continuously with a modified ventilator (Dräger, Lübeck, Germany). Arterial blood gases were analyzed after placement of catheters and every 30 minutes during reperfusion. At this interval, pulmonary vascular resistance (PVR) was calculated after measurement of cardiac output with the thermodilution catheter (COM2 cardiac output computer, Baxter).

Surfactant analysis. Bronchoalveolar lavage (BAL) fluid was obtained from the right lower lobe in all experiments after catheter placement by means of 100 mL of saline solution. A second BAL was performed after 2 hours of reperfusion of the left lower lobe. The lavage fluid was immediately centrifuged at 270g, and the cell-free supernatant was frozen at -80°C. A surfactant pellet was resuspended in saline solution supplemented with 1.5 mmol/L calcium chloride. Pellet and supernatant were separated at 27,000g for 30 minutes. Protein and phospholipid content were determined according to the method of Bartlett.¹¹ Small and large aggregates were separated, and their weight was expressed as a small/large aggregates quotient. Surfactant function was determined by means of a pulsating bubble surfactometer (Electronetics, Buffalo, NY) according to the technique described by Enhornig¹²: 40 µL of large aggregate suspension, which had been adjusted to a phospholipid concentration of 1 mg/mL, was filled into the sample chamber. The surface tension at minimal bubble size (γ_{min}) was obtained after 5 minutes of bubble pulsation at a rate of 20 cycles/min and a temperature of 37°C. Before bubble pulsation was started, the initial surface tension after bubble formation was measured, and the adsorption rate was determined as surface tension 10 seconds after formation of a bubble. All analog data were digitalized and recorded by a personal computer.

Fig 1. Survival after reperfusion of the left lung and clamping of the right lung in percentage of animals per group.

Lung water content. Specimens of the left lower lobe were obtained after termination of the experiment. Wet and dry weight were measured, and water content was expressed as a percentage of wet weight.

Animal care. All animals received humane care 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 National Academy of Sciences and published by the National Institute of Health (National Institutes of Health publication No. 80-23, revised 1985).

Statistical analysis. All data are expressed as means $\pm$ SE. Intergroup analysis of continuous data were performed from 0.5 to 2.0 hours of reperfusion by repeated-measures analysis of variance. For data without repeated measurement, 1-way analysis of variance was applied. All data were analyzed with the Statistical Program of Social Sciences (SPSS for MS Windows version 6.1, SPSS, Inc, Chicago, Ill).

Results

Right heart failure developed within 3.58 ± 0.4 hours of reperfusion (95% confidence interval, 2.81-4.36) in the group receiving EC solution (Fig 1). All animals required inotropic support after clamping of the right pulmonary artery throughout the reperfusion period. Three minipigs died within 3.5 hours of reperfusion. No animal survived the observation period of 7 hours. During the first 2 hours of reperfusion, a decrease in oxygen tension/inspired oxygen fraction (PO_2/FiO_2)

Fig 2. PO_2/FiO_2 of lungs preserved with LPD and EC solution before flush perfusion (basal) and after 0.5 to 7 hours of reperfusion with clamping of the contralateral lung.

from 558 ± 33 to 227 ± 85 mm Hg (Fig 2) was found. After clamping of the right bronchus, dynamic compliance declined (Fig 3) from 21.7 ± 0.9 to 11.3 ± 2.5 mL/mm Hg and remained in that range for the reperfusion period. PVR increased after clamping of the right lung from 330 ± 77 dynes $\cdot$ s $^{-1}$ $\cdot$ cm $^{-3}$ to 648 ± 102 dynes $\cdot$ s $^{-1}$ $\cdot$ cm $^{-3}$. A further increase was found after 60 minutes of reperfusion (961 ± 133 dynes $\cdot$ s $^{-1}$ $\cdot$ cm $^{-3}$). Thereafter, PVR remained stable until the onset of right heart failure, when high PVR was calculated at cardiac outputs of less than 0.5 L/min (Fig 4).

In the group receiving LPD solution, all animals survived the observation period of 7 hours ($P = .0001$). All minipigs of the LPD group received inotropic support for 30 to 60 minutes after clamping of the pulmonary artery. No inotropic agents were required thereafter. PO_2/FiO_2 dropped from 585 ± 57 mm Hg at the onset of reperfusion to 382 ± 85 mm Hg after 2 hours and 290 ± 79 mm Hg after 7 hours. In comparison with the EC group, the oxygenation index was significantly higher in the LPD group ($P = .034$). Dynamic compliance of the LPD solution-treated minipigs declined from 25.3 ± 2.2 to 18.7 ± 1.5 mL/mm Hg after clamping and to 17 ± 1.0 mL/mm Hg after 7 hours. Compliance (Fig 3) was higher compared with that found in the EC group ($P = .0005$). In the LPD group, PVR rose similar to the EC solution-treated animals to 928 ± 178 dynes $\cdot$ s $^{-1}$

Fig 3. Dynamic compliance of lungs preserved with LPD and EC solution before flush perfusion (*basal*) and after 0.5 to 7 hours of reperfusion with clamping of the contralateral lung.

Fig 4. Pulmonary vascular resistance (*PVR*) of lungs preserved with LPD and EC solution before flush perfusion (*basal*) and after 0.5 to 7 hours of reperfusion with clamping of the contralateral lung.

$\cdot \text{cm}^{-3}$ after clamping of the right pulmonary artery and remained stable until termination of the experiments (Fig 4).

Lung water content of the reperfused lung at termination of the experiment was $89.4\% \pm 0.9\%$ in the EC group. Because of longer survival, specimens of the LPD group were obtained later. The lung water content was significantly lower ($80.6\% \pm 3.5\%$, $P = .049$).

Surfactant analysis. When comparing minimal surface tension of the BAL fluid before ischemia (right lung), after ischemia, and after 2 hours of reperfusion (left lung) in the group receiving EC solution (Fig 5), a remarkable increase was found after reperfusion. Concomitant with this finding was a higher protein content (Fig 6) and an increase of the ratio of surface nonactive small aggregates and the active surface large aggregates of the BAL fluid (Fig 7).

A similar pattern was observed for the group receiving LPD solution: minimal surface tension (Fig 5) did increase after reperfusion, as did protein concentration of the BAL fluid (Fig 6) and the small aggregates/large aggregates ratio (Fig 7). Comparing with EC solution-perfused lungs, minimal surface tension of the LPD group was comparable before ischemia but significantly lower after reperfusion ($P = .02$). In comparison with the EC group, protein concentration in the LPD group was similar before ischemia; however, significantly lower levels were obtained after reperfusion

($P = .015$). The small aggregates/large aggregates ratio was comparable in the 2 groups before ischemia. A 3-fold increase after reperfusion was observed for the LPD solution-perfused lungs (Fig 7). Higher small aggregates/large aggregates ratios were found for the EC group after reperfusion ($P = .07$).

In terms of phospholipid concentration of the lavage fluid, $60.3 \pm 5.64 \mu\text{g/mL}$ was found before ischemia in the group receiving EC solution, and $74.95 \pm 9.77 \mu\text{g/mL}$ was found in the minipigs receiving the LPD solution ($P = .3$). The concentrations were $74.95 \pm 8.84 \mu\text{g/mL}$ (EC solution) and $85.52 \pm 18.1 \mu\text{g/mL}$ (LPD solution, $P = .6$) after reperfusion.

Discussion

The introduction of flush perfusion with EC solution allowed for clinical lung preservation up to 6 to 8 hours.¹³ It has been successfully applied for more than a decade and has become the most often used preservation method of the lung. However, reperfusion injury remains a significant problem in lungs preserved with EC solution in the early post-transplantation period.¹⁴

The biochemical rationale of this solution of intracellular ion composition lies in the reduction of potassium leakage of the preserved cells, leading to less intracellular edema.¹⁵ However, cytotoxicity of potassium was found to impair endothelial cells,⁵ as well as type II pneumocytes,⁷ of the lung. In this study of preserva-

Fig 5. Minimal surface tension of BAL fluid in milli-Newtons per meter, as determined with a bubble surfactometer. Results are shown before flush perfusion of the right lungs (*basal*) and after 2 hours of reperfusion of the left lungs.

tion, warm ischemia, and reperfusion of the lung, lethal reperfusion injury was induced in the EC solution group. This was characterized by deteriorating lung function and right heart failure independent of any immunologic response to an allograft. Surfactant analysis after 2 hours of reperfusion revealed a significant increase of minimal surface tension and thus a lack of adequate surfactant function. Concomitant with this finding was a reduction of dynamic lung compliance. In contrast, cardiopulmonary function remained stable in the LPD solution group. Adequate surfactant function was maintained in this group, as was demonstrated by surfactant analysis after 2 hours of reperfusion and stable dynamic lung compliance throughout the experiment.

Limitations of this study are the use of warm ischemia in contrast to cold ischemia in clinical lung transplantation and the absence of immunologic responses to an allograft. Compared with other preparations of isolated cells, ex vivo perfused organ models, and allotransplantation models in small animals, the

Fig 6. Protein concentration of BAL fluid in milligrams per liter. Results are shown before flush perfusion of the right lungs (*basal*) and after 2 hours of reperfusion of the left lungs.

use of our model has the advantage of a cardiopulmonary circulation similar to that of human subjects. Interactions of the pulmonary circulation and right heart function resemble the clinical situation in single lung transplantation. A further advantage of this model is the avoidance of donor animals, thus reducing the number of minipigs required by 50%. Short-term warm ischemia develops very rapidly and induces severe reperfusion injury at a reliable rate in EC solution-preserved lungs, as was known from earlier experiments with this model.¹⁶ This induction of lung failure resembles clinical graft failure after lung transplantation in reduction of compliance, gas exchange, and increase of PVR. Whether the impairment of surfactant function follows the same pattern is likely but not verified.

Plasma proteins, such as albumin and hemoglobin, are widely known inhibitors of surfactant function.¹⁷ The loss of surfactant function in the EC solution group is most certainly the result of inhibition caused by plasma proteins leaking into the alveoli. This hypothesis is supported by the findings of increased protein content

of the BAL fluid after reperfusion and the increase of the small aggregates/large aggregates ratio, indicating a decrease of surface active large aggregates and an increase of nonactive small aggregates. In contrast, in the LPD solution group, protein content of the BAL fluid did not increase during reperfusion, and the small aggregates/large aggregates quotient did not rise. Surfactant function remained stable in this group. In addition, lung water content was significantly lower in the LPD group than in the EC group at the end of the experiments. These findings indicate a reduction of lung edema formation caused by preservation with LPD solution with less plasma protein leakage into the alveolar space. Therefore, surfactant inhibition did not occur to the same extent as in the EC group.

In human lung transplant recipients of EC solution-perfused grafts, severe impairment of biophysical surfactant function was found, as well as an increase of the small aggregates/large aggregates ratio¹⁸ in the early postoperative course. This dysfunction may account in part for an impairment of graft function. In animal experiments,^{19,20} as well as in clinical cases,¹⁰ early postoperative graft dysfunction was successfully improved by administration of surfactant preparations. The question remains of whether the surfactant dysfunction of EC solution-perfused and transplanted lungs is only attributable to an inactivation of surfactant by plasma proteins or if surfactant generation is also disturbed. Studies of isolated type II pneumocytes revealed less cellular edema and less damage to the nuclear membrane when stored in LPD solution compared with University of Wisconsin solution, another intracellular-type high-potassium solution.²¹ In addition, a higher metabolic activity of type II pneumocytes was found when stored in LPD rather than in EC solution.⁷ This indirect evidence of a disturbed type II pneumocyte function after EC solution storage is strengthened by the fact that surfactant function did not recover in the long-term follow-up after clinical lung transplantation.¹⁸ However, the degree of vascular leakage of plasma proteins into the alveolar space may be the most important mechanism of reduction of surfactant function in the reperfusion period. In part, the vascular leakage may be due to an impairment of endothelial and smooth muscular function of the pulmonary vessels. In an earlier study with the same model, a similar improvement of lung function and surfactant activity was shown with the supplementation of a surfactant preparation before reperfusion.²² However, with surfactant administration, an increase of protein concentration of the BAL fluid after reperfusion could not be prevented in lungs preserved in EC solution. Most

Fig 7. Small aggregates/large aggregates ratio of BAL fluid. Results are shown before flush perfusion of the right lungs (basal) and after 2 hours of reperfusion of the left lungs.

solutions used clinically for lung preservation, such as EC solution or University of Wisconsin solution, are high potassium-containing intracellular-type solutions. Despite this fact, no clinical study was published revealing superiority of these solutions when compared with low-potassium extracellular-type solutions. A body of evidence was established of the injurious effects of high-potassium solutions on endothelial cells, as well as epithelial cells. Because safe preservation of lungs with excellent pulmonary function was demonstrated in a pig model²³ of single lung transplantation, our experiments revealing improved surfactant function after ischemia and reperfusion, as well as numerous other studies indicating improved preservation quality of LPD solution, suggest that clinical use of LPD solution should be considered. It remains to be shown by clinical data whether LPD solution does indeed reduce reperfusion injury after clinical lung transplantation and improve surfactant function. In addition, further studies are required to reveal protective measures of surfactant function after lung transplantation with respect to long-term graft function.

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