Restitution of impaired lung allograft function with extracorporeal membrane oxygenation (ECMO)

Ph.D. Thesis

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Budapest / Vienna 2011

1. INTRODUCTION

According to the report of the International Society for Heart and Lung Transplantation, primary pulmonary graft dysfunction (PGD) accounts for almost one third of early deaths. According to our current knowledge PGD is a result of repetitive traumatic episodes to the allograft. Main contributors are brain death, preservation and storage conditions, and the effects of reperfusion.
PGD 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, due to over inflation and further elevation of pulmonary arteriolar pressure.
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 as well as experimental reports.
The first data on the importance of controlled reperfusion was derived from experimental studies. Okamoto and Allen demonstrated that 20 min of controlled reperfusion are superior to 10 min only after regional ischemia in hearts. Halldorsson and Bhabra proved, that reduction of pulmonary artery pressure during the first 10 min of reperfusion of transplanted lungs, leads to a clear reduction in the severity of pulmonary reperfusion injury. There are however no experimental data available, whether a substantial prolongation of such a controlled reperfusion period could be of further benefit.
Additional information about the importance of controlled reperfusion comes from clinical experience with bilateral sequential lung transplantation performed without cardiopulmonary bypass (CPB). During this procedure, the first transplanted lung is subjected to the complete cardiac output during the implantation of the second one. As a consequence, tissue edema formation and radiographic infiltrates in the first transplanted lung are common and known as the "first lung syndrome". For these reasons, some centres prefer to perform bilateral lung transplantation (BLTX) routinely on CPB, which offers the possibility for improved reperfusion conditions especially to the first lung.
Similar results derive from the experience with ex vivo lung assessment. Steen and colleagues investigated lung allografts of non-heart-beating donors (NHBD) after preservation with topical cooling. They reported about the importance of keeping the pulmonary artery pressure below 20 mmHg during the functional assessment of the grafts by ex vivo perfusion. The same principle was applied by Egan et al. for ex vivo assessment of human lungs. All this data suggests that the

reduction of pulmonary artery flow during the early reperfusion is crucial for the prevention of severe reperfusion injury. However, the optimal length of time to provide such reperfusion conditions remains undefined so far.

The importance of such a low pressure, low tidal volume ventilation for prevention of lung damage as well as for recovery of already injured lungs has been demonstrated repeatedly. Traditional approaches to mechanical ventilation use tidal volumes of 10–15 ml per kg of body weight. In animal experiments, it has been demonstrated that ventilation with such large tidal volumes causes disruption of the pulmonary epithelium and endothelium and subsequently leads to lung inflammation and release of inflammatory mediators. These experimental findings are in line with clinical observations. In a controlled, multicentre randomized trial of the acute respiratory distress syndrome (ARDS) network on 861 patients with acute lung injury or ARDS, the authors were able to demonstrate that a less aggressive respiratory pattern with lower tidal volumes than traditionally used resulted in improved clinical outcome. This data supports the view that aggressive ventilation patterns – although sometimes necessary to provide adequate oxygenation – contribute to exacerbation and perpetuation of lung injury itself.

ECMO has been used in a wide spectrum of indications, including clinical lung transplantation and treatment of severe lung injury. Recently, its efficiency for treatment of severe forms of ARDS, has been described. In this situation, ECMO maintains gas exchange and provides optimal conditions for lung recovery, by allowing the use of non-damaging ventilator settings. A similar approach, based on the concept "to put the lung to rest", in order to achieve better conditions for recovery, was described by Iglesias and co-workers. They used near-static ventilation for severe ARDS patients while providing gas exchange over a pumpless extracorporeal membrane system (Novalung).

In lung transplantation both, controlled low pressure perfusion and low tidal volume ventilation can be provided by v/a ECMO. Usually ECMO is applied for treatment of already established graft failure. However, it can also be used already intraoperatively as an alternative to CPB and then be prolonged into the postoperative period, to provide optimal reperfusion conditions to the transplanted allograft. Ko et al. reported their experience in five patients with PPH, where they used ECMO during LTX and for several hours thereafter. All patients had an uneventful TX and showed an excellent organ function after the procedure. Our own early experience with LTX on intra- and postoperatively prolonged ECMO was gained from patients with severe pulmonary hypertension. 17 patients underwent transplantation in this way and initial organ function was excellent in all of them.

Following this experience, we later on expanded the use of ECMO for LTX in our department until it finally replaced the use of CPB as standard method completely. From our own early experience, we were impressed by the observation, that the transplanted lungs that were in even very severe forms of reperfusion edema, were able to recover within a short period of time once venoarterial ECMO was installed. In our clinical experience with this approach, we have seen excellent initial graft function even with the use of very marginal donor organs.
From all these reports it becomes evident that v/a ECMO treatment not only maintains vital functions during periods of severe lung injury, but even more, directly contributes to improved recovery of the lung by these two factors: reduction of pulmonary artery flow and avoidance of harmful ventilator settings.
However, it is certainly difficult to evaluate this clinical experience on an objective basis, given the heterogeneity of clinical situations. For this reason, we decided to test the validity of the hypothesis, in a standardized experimental model of severely injured lung allografts.

2. STUDY AIM

The aim of our research was therefore to investigate the effect of intraoperative and prolonged postoperative v/a ECMO support on the early allograft function of critically injured donor lungs in an experimental large animal transplant model comparable with the human clinical setting.

3. MATERIAL AND METHODS

The study was performed in accordance to the Austrian Animal Research Statute (1988), and was approved by the Local Ethical Committee of the Medical Faculty, University of 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 Use of Laboratory Animals“, prepared by the National Institutes of Health (NIH publication 96-03, revised 1996).

2.1.Experimental groups

32 healthy pigs (German Large White) were used. 16 served as brain death donors, 16 served as recipients. 4 hours after induction of brain death the donor

lungs were harvested and stored for a cold ischemic period of 22 hours. The transplant procedure was a left single lung transplantation followed by cross clamping of the right lung 1 hour after reperfusion.
The 16 recipient pigs were divided into 2 groups:

Group A: 8 pigs transplanted without ECMO support using standard postoperative ventilation with 10 ml/kgBW.

Group B: 8 pigs transplanted with intra- and postoperative (22 hours) ECMO support receiving protective low tidal volume postoperative ventilation with 5 ml/kgBW.

Functional assessment was performed 10 minutes after exclusion of the contralateral right lung (Time point 1=TP 1), 1 hour later (Time point 2=TP 2), and 22 hours later in group B (i.e. 1 hour after weaning from ECMO, Time point 3=TP 3). Graft function was compared between both groups by measuring oxygenation, pulmonary artery pressure, dynamic lung compliance and extravascular lung water content (wet to dry ratio) (Figure).

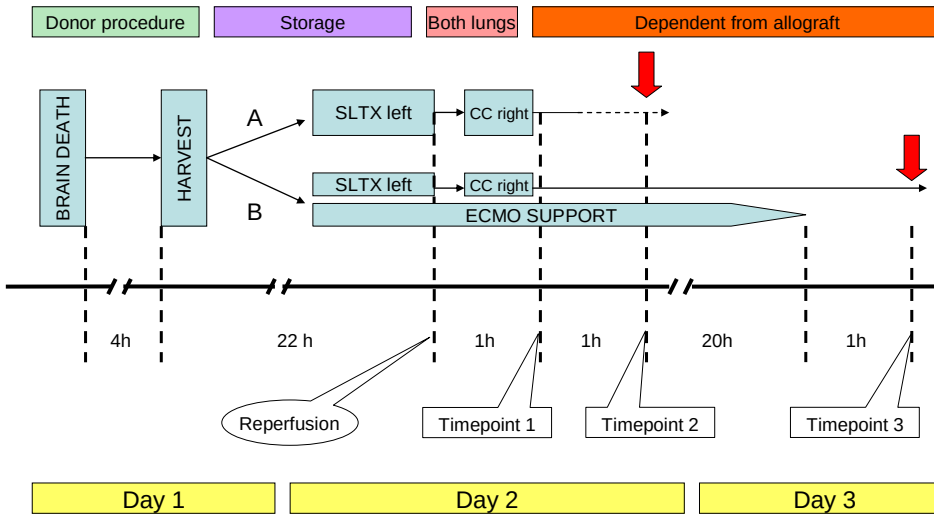

Figure: Experiment flowchart (CC right= cross clamping the right lung, SLTX = single lung transplantation)

2.2. Donor procedure

2.2.1. Anesthesia:

Arterial line for invasive pressure monitoring (Smiths Medical, Germany) was placed in the right internal carotid artery. Venous line for drugs and fluid replacement was placed in the internal jugular vein. For introduction of a Swan-Ganz catheter (size 7.5 F, Vigilance, Edward Lifesciences; USA) 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 Ketamin (Ketavet, Pharmacia Upjohn) + 1,76 mg/kg Acepromazin (Vanastress, Vana, Austria) IM. Anaesthesia was introduced with 15 mg/kg Thiopental, 15 mg Piritramid (Dipidolor, Janssen-Cilag Pharma,

Austria), and 20 mg Rocuroniumbromid (Esmeron, Organon, Netherlands) IV and maintained with 0,1 mg/kg/h Piritramid, 10 mg/kg/h Propofol (Propofol Fresenius 2%, Fresenius Kabi, Austria) and 0,1 mg/kg/h Rocuroniumbromid IV for muscle relaxation. All animals were fully heparinised with 300 IU/kgBW Na-Heparine (Heparin Immuno, EBEWE Pharma, Austria) IV, given before cross clamping of the aorta. Animals were intubated with an endotracheal tube Ch 8 (Rüsch, Germany) and ventilator (Dräger Primus, Dräger Lübeck, Germany) settings were put as follows: TV 10ml/kgBW, f 20/min, FiO_2 0,5 – 1,0, I:E 1:2, PEEP 5 cmH_2O, respectively, with an $ETCO_2$ target value of 40mmHg.

2.2.2. Brain death procedure:

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

2.2.3. Lung harvesting:

In contrast to the clinical routine, donor animals did not receive steroid medication to avoid any possible impact 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 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 ante grade flush of 50 ml/kg cold low-potassium dextran solution (LPD) (Perfadex®, Vitrolife, Gothenburg, Sweden) supplemented by 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 heart and lungs together with the esophagus was performed, and prior to 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 LPD solution, and stored at 4°C for 22 hours.

2.3. Recipient procedure

2.3.1. Anesthesia:

Anesthesia for the recipient animals was identical as for the donor pigs. One single dose of 5,000 IU Na-Heparin and 500 mg Imipenem (Tienam, Merck Sharp & Dohme, Netherlands) IV was administered. Immunosuppression consisted of one single IV dose of 500mg Methylprednisolone (Solu-Medrol, Pharmacia Upjohn, Belgium) given immediately prior to reperfusion.

2.3.2. Implantation

The donor lung was then reimplanted using 4-0 PDS running sutures for the bronchial anastomosis and 5-0 Prolene sutures for the pulmonary artery and the left atrium. The implanted lung underwent retro- and antegrade de-airing and flushing according to standard procedures. Thereafter, the arterial clamp was partially released for 10 minutes in order to provide controlled reperfusion. 1 hour later, the bronchus and artery of the contralateral right lung were cross-clamped. Ventilation to the transplanted lung was begun during reperfusion by the standard method in Group A and by using low tidal volumes in Group B. At the end of the experiments, animals were sacrificed by clamping of the left pulmonary artery.

2.3.3. ECMO management

For the animals in Group B, the Medtronic Biomedicus portable bypass system with a hollow fibre oxygenator (Medtronic CPMPCB Affinity BPX-80, Medtronic, Minneapolis, MN, USA) with 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 Ringer´s Lactate solution. The flow was set on 50% of initial CO. This support was maintained throughout the whole TX procedure and continued for a further 22 hours. Thereafter the pig was gradually weaned from ECMO. 1 hour later the final functional assessment (Time point 3) was performed.

2.3.4. Assesments

All arterial blood gas samples were taken from the right internal carotid artery after a test ventilation period of at least 10 minutes at FiO_2=1,0 (ABL800 Flex Radiometer Copenhagen, Denmark). Heart rate, arterial blood pressure, oxygen saturation, central venous pressure and pulmonary artery pressure were continuously monitored (PPG Hellige, Germany). Dynamic compliance was measured using a volume controlled ventilator (Dräger Primus, Drägerwerk Lübeck, Germany). Lung biopsy samples were taken from the anterior margin of the lower lobe. The piece of the biopsy was weighed and then dried to a constant weight at 80^0C. Lung water was calculated using the following formula: % tissue water = ((wet weight-dry weight) / wet weight) x 100.

We checked the distributions of all variables for symmetry by comparing means to medians and ranges, and found no unusually skewed distributions. Therefore, animal characteristics were described by mean and standard deviation and compared between groups using independent samples t-tests. Outcome measures were compared between groups using repeated measures analysis of variance (RM-ANOVA) specifying a first-order autoregressive covariance structure. An interaction of group with time was assessed, and if the interaction was significant, Bonferroni-Holm corrected p-values comparing groups at different time points were computed. Otherwise, the group difference was assumed to be equal across all time points and a common p-value was computed from the RM-ANOVA model. This analysis was repeated, replacing original values by their ranks, to see whether results depended on the assumption of normal distribution. There was no difference in the pattern of significances between both analyses suggesting robust results. There were also no relevant changes by specifying different types of covariance structures. Survival was compared using the exact log-rank test (11). All tests were two-sided. The SAS System v9.2 (2008 SAS Institute Inc., Cary, NC, USA) was used for statistical computations.

4. RESULTS

There was no important difference between both study groups regarding baseline variables.

4.1. Survival:

Survival was better in Group B than in Group A (100% vs. 50% at time point 2; $p = 0.026$).

Group A: All animals died due to lung edema and hypoxia. 1 pig died 28 minutes after reperfusion and did not reach time point 1. 3 other pigs died before time point 2. From the remaining 4 pigs, 2 died immediately after time point 2 and the others 3 hours later.

Group B: All animals survived and were successfully weaned from ECMO after 22 hours except one. This animal showed critical hemodynamical instability after 3 weaning attempts, however without signs of lung edema. The other 7 pigs remained in stable condition after time point 3 and no trend of deterioration was observed over the following 3 hours. Thereafter the experiments were terminated.

4.2. Functional performance:

4.2.1. Oxygenation:

There was no difference between Group A and Group B regarding P/F ratio neither after reperfusion (291±88 mmHg versus 338±73 mmHg, respectively, $p>0.2$), nor 10 minutes after becoming dependent from the allograft (Timepoint 1) (137±148 versus 150±87mmHg, respectively, $p>0.2$). At timepoint 2, mean P/F ratio of the surviving 4 animals in group A was worse than in Group B (96±41 versus 178±114 mmHg, $p>0.2$). 1 hour after weaning from ECMO (Timepoint 3) pigs in Group B showed excellent allograft function (323±129 mmHg). When the corresponding values for 1 hour dependency from the new lung in the two groups (group A: Timepoint 2, group B: Timepoint 3) were compared, better results were seen in group B (96±41 mmHg versus 323±129 mmHg, $p=0.002$).

4.2.2. Pulmonary artery pressure

Mean PAP was higher in Group A than in Group B both after pneumonectomy and immediately after reperfusion (28.5±4.5 mmHg versus 18.6±3.9 mmHg, p=0.002 and 28.9±7.2 versus 18.8±2.1, p=0.002, respectively). At timepoint 1, there was also some difference in mean PAP values between Group A and Group B (38.4±7.7 versus 32.9±7.1 mmHg, p=0.048, respectively). At timepoint 2, mean PAP of the surviving 4 animals in group A was higher than in Group B (45.3±4.1 versus 33.6±4 mmHg, p=0.006). 1 hour after weaning from ECMO (Timepoint 3) pigs in Group B showed almost normal mean PAP (24.1±5.4 mmHg). Again, when comparing this value with mean PAP at timepoint 2 in Group A (45.3±4.1), the difference is highly in favor for Group B (p<0.001).

4.2.3. Lung compliance

At timepoint 1 compliance was 16±8 ml/cmH_2O in Group A versus 13±3 ml/cmH_2O in Group B (p>0.2), at timepoint 2 11±1 ml/cmH_2O versus 14±3 ml/cmH_2O, respectively (p>0.2). Again, comparing compliance of Group A at timepoint 2 with compliance of Group B at timepoint 3, the allografts in the ECMO Group performed better (11±1 ml/cmH_2O versus 16±5 cmH_2O, p>0.2).

4.2.4. Wet-to-dry ratio

Differences between study groups regarding lung water content could be due to chance. Wet-to-dry ratio was 82.7±4.2% in Group A versus 76.0±7.4% in Group B at timepoint 1 (p>0.2), 78.5±3.5% in Group A versus 76.8±5.3% in Group B at timepoint 2(p>0.2), and 76.9±9.1% in Group B at timepoint 3.

5. CONCLUSIONS

In this model, the combined injury by brain death with a prolonged ischemic time of 22 hours uniformly resulted in the development of severe PGD in group A, where lungs were transplanted in a conventional way. The addition of brain death in our donors obviously contributed significantly to the resulting severe organ damage, since Steen and colleagues, in a similar setting, but without brain death, reported a by far better functional performance of their donor lungs. Assessments in this experiment were performed in accordance to the time points of clinical importance, which are 10 minutes after crossclamping of the contralateral lung (time point 1) and 1 hour thereafter (time point 2). Since animals in group B at that time were under partial ECMO support, they were also

investigated at time point 3 (1 hour after weaning from ECMO, i.e. after complete dependency on the transplanted lung). In order to compare the situation of 1 hour of complete dependency on the transplanted lung in both groups, and since none of the animals of group A survived long enough to reach time point 3, results from TP 3 in group B were also compared to results from TP 2 in group A. The results obtained with this setting were striking. All animals of group A developed severe reperfusion edema and died before or soon after time point 2. In contrast to that, all except one of the animals in group B were successfully weaned from ECMO and showed excellent graft function, which was maintained for several hours more. The one animal that could not be weaned from ECMO got instable due to hemodynamical problems and not due to development of PGD. This finding was paralleled by clearly superior functional parameters in group B.

According to these findings we conclude, that:

1. The importance of reperfusion conditions after lung transplantation and the length of the critical time period have been underestimated so far. However, the exact time period needed for lung recovery due to ischemic injury remains undefined. Obviously, it clearly exceeds the always described period of the first 10 to 15 minutes after transplantation. This period of 22 hours is obviously sufficiently long enough that the graft can recover from the injury obtained during brain death and ischemic storage and can provide excellent organ function thereafter. Based on our clinical and experimental experience, this time period should be 8-12 hours, if dealing with early signs of PGD and using ECMO in a pre-emptive manner, and between 24-48 hours, if treating manifest PGD. . In order to avoid further damage from barotrauma and hemodynamic instability from maximal ventilatory support, ECMO should be applied early in the course of lung dysfunction after transplantation.

2. Prolonged v/a ECMO support can provide additional safety for transplantation of marginal donor lungs and therefore might help to expand the current organ donor pool.

3. Prolonged controlled reperfusion and protective ventilation strategies provide a valuable addition to current own and worldwide efforts of ex vivo reconditioning of donor lungs.

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7. AKNOWLEDGEMENTS

Many thanks to

my parents,
they provided me with everything I ever needed in my medical career,

my wife Csilla,
she inspired me over the many years and provided a wonderful family background for my profession,

my children Patrik, Christian and Cecilia,
they had master their life so often without papa´s support,

my mentor Walter Klepetko,
he introduced me into the world of transplantation,

my colleague Ferenc Rényi-Vámos,
true all the many late nights of surgery we have became true friends.