Aprotinin decreases reperfusion injury and allograft dysfunction in clinical lung transplantation

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Abstract

Objective: Primary graft dysfunction caused by ischemia–reperfusion injury is one of the most frequent causes of early morbidity and death after lung transplantation. We hypothesized that the perioperative management with aprotinin decreases the incidence of allograft reperfusion injury and dysfunction after clinical lung transplantation. Methods: Lung transplant databases of two transplant centers were used to investigate the incidence of severe post-transplant reperfusion injury (PTRI). We examined data of 142 patients who underwent either single lung (81) or bilateral sequential lung (61) transplantation for COPD, idiopathic pulmonary fibrosis, cystic fibrosis, and miscellaneous lung disorders between 1997 and 2000. Thirty patients were excluded due to heart–lung transplantation or lung transplantation for Eisenmenger’s disease, re-transplantation, rejection, or deviation from the standardized triple immunosuppression protocol. The data of remaining 112 patients (control group, 64% single lung, 36% sequential bilateral lung transplants) were compared to the prospectively collected data of 59 lung transplant patients over the last 5 years. All of these 59 patients were managed perioperatively with aprotinin infusion. In addition, Euro-Collins-aprotinin procurement solution (Apt-EC group) was used for 50 donor lungs (58% single lung, 42% sequential bilateral lung transplants). Aprotinin in combination with low-potassium dextran (LPD) flush solution (Apt-LPD group) was used for the procurement of 34 lungs (59% single lung, 41% sequential bilateral lung transplants). The International Society of Heart and Lung Transplantation (ISHLT) grade III injury score was used for the diagnosis of severe PTRI, which is based on a PaO₂/FIO₂ ratio of less than 200 mmHg. Results: Severe reperfusion injury grade III was observed in 18% of the control group. ECMO support was required in 25% of these patients. The associated mortality rate was 40%. Correlating factors for PTRI were donor age greater than 35 years (45%, \( p = 0.01 \), mean age 38 ± 8) and recipient pulmonary artery systolic pressure greater than 60 mmHg (48%, \( p < 0.05 \)). Lung graft ischemic times (231 ± 14 min) and intraoperative techniques (cardiopulmonary bypass in 12%) were not associated with negative outcomes. Despite longer ischemic times (258 ± 36 min and 317 ± 85 min, respectively) and older donors (42 ± 12 years and 46 ± 12 years, respectively) in the aprotinin patient groups (Apt-EC and Apt-LPD group), the incidence of PTRI was markedly lower (6% and 9%, respectively). There was no mortality in the Apt-EC group and one patient died in the Apt-LPD group due to PTRI-induced graft failure. Conclusions: Severe PTRI increased short-term morbidity and mortality. The incidence of reperfusion injury was not dependent upon the duration of donor organ ischemia. The use of aprotinin in the perioperative patient management in lung transplantation had strong beneficial effects on the patient outcomes and decreased the incidence of post-transplant ischemia–reperfusion injury significantly.

Keywords: Clinical lung transplantation; Ischemia–reperfusion injury; Graft failure

1. Introduction

Lung transplantation has become the standard of care for end-stage lung diseases. It is a widely accepted therapeutic option for patients who are otherwise refractory to medical therapy. Lung transplantation is now carried out on a routine basis with low operative mortality. The immediate success of lung transplantation is directly related to the incidence of primary graft dysfunction, which is a primary cause for early morbidity and mortality [1]. Ischemia and the subsequently developing reperfusion injury are considered to be the principal mechanisms leading to early graft dysfunction. In the light of a significant organ shortage leading to more relaxed organ acceptance criteria and the increasing use of marginal donors, the optimization of lung allograft function is currently the most important management issue in lung transplantation. Aprotinin is a serine-protease inhibitor that is already widely used in clinical cardiovascular surgery. It demonstrates strong protective and anti-inflammatory properties by suppressing the release of lysosomal enzymes and
inhibiting neutrophil activation. Experimental studies revealed improved lung transplant function following the addition of aprotinin to standard crystalloid preservation solutions [2]. However, the benefits of aprotinin in lung transplant recipients have not been clearly demonstrated as of yet.

Therefore, the purpose of this study is to examine the incidence of ischemia—reperfusion injury in lung transplantation and to investigate the protective effects of aprotinin on primary graft function in clinical lung transplantation.

2. Material and methods

We performed a retrospective chart review of 142 lung transplant recipients at two medical centers to determine the incidence of reperfusion injury and its impact on outcomes between 1997 and 2000. These patients were compared to 59 lung transplant patients who underwent lung transplantation between 2000 and 2005 and who were perioperatively managed with aprotinin, a serine-proteinase inhibitor (Trasylol; Bayer Pharmaceuticals, West Haven, CT, USA). Thirty patients were excluded from the data analysis because of clinical incompatibility such as lung re-transplantation (n = 7), heart—lung transplantation (n = 8), lung transplantation for primary pulmonary hypertension (n = 7), lung transplantation for Eisenmenger’s syndrome (n = 6), and living-lobar transplantation (n = 1). One more patient was excluded due to the diagnosis of hyperacute rejection and significant HLA-mismatch [3]. This patient was managed with a complex immunosuppressive regimen deviating significantly from the standard protocol. The standard recipient immunosuppressive protocol was a triple medication regimen consisting of glucocorticoids, cyclosporine, and azathioprine or glucocorticoids, cyclosporine, and mycophenolate mofetil. The immunosuppressive medications were started 4—6 h pre-operatively in all recipients. Organ procurement and storage were performed with hypothermic crystalloid flush solutions in all patients. Euro-Collins (EC) solution (Baxter Healthcare Corp., Deerfield, IL, USA) was used for 112 lung transplant recipients. The data of these 112 patients (control group) were compared to the prospectively collected data of 59 patients who underwent lung transplantation for similar end-stage lung diseases and additionally, received aprotinin infusion perioperatively. Aprotinin was administered by means of a central venous line according to the following regimen: following an aprotinin test dose, the loading dose of 280 mg aprotinin (or 2 million kallikrein inhibiting units) was infused, followed by 500,000 kallikrein inhibiting units (KIU) per hour constant infusion for the duration of surgery. In the case of cardiopulmonary bypass supported lung transplantation, additional 2 million KIU were added to the prime solution.

This study was designed to investigate the perioperative anti-inflammatory properties of aprotinin and their impact on mid-term outcomes. The blood-saving effects of aprotinin are well documented in cardiovascular surgery; however, they are not the subject of this investigation. Like in many other lung transplant centers observed, a very liberal blood product administration policy is applied in our lung transplantation unit postoperatively which means the frequent usage of packed red blood cells and fresh frozen plasma for intravascular volume expansion even if the hematocrit is greater than 30% and no postoperative bleeding is observed. This protocol assists in managing the frequently encountered leaky capillary syndrome of lung transplantation patients, in which the administration of crystalloid or colloid-like albumin fluid solutions would immediately accumulate within the interstitial and alveolar spaces leading to aggravation of the ischemia—reperfusion syndrome. Therefore, in our unit, lung transplant patients have a very high likelihood of receiving blood products for multiple reasons, making the analysis of aprotinin-related blood product saving capabilities impossible.

For 35 of the 59 aprotinin-managed lung transplant recipients (50 donor lungs for 20 single and 15 bilateral sequential lung transplants) EC flush solution was used together with 2 million KIU aprotinin for organ procurement (Apt-EC group). The remaining 24 of the 59 aprotinin lung transplant recipients received 34 donor lungs (14 single and 10 bilateral sequential lung transplants) in combination with low potassium dextran solution (LPD, Vitrolife, Gottenberg, Sweden) as well as 2 million KIU aprotinin for lung procurement and graft storage (Apt-LPD group).

Applying the International Society of Heart and Lung Transplantation (ISHLT) working group definition, we classified recipients as having ISHLT grade III (severe) primary graft dysfunction (PGD) if the lowest $P_{aO_2}/F_{O_2}$ ratio within 48 h post-transplant was less than 200 with $F_{O_2}$ being the fraction of inspired oxygen, and $P_{aO_2}$ the arterial oxygenation [4]. As chest X-rays were not consistently available to be read and compared, this information was not incorporated. Data collected regarding the donor included age, gender, mechanism of death, and allograft ischemic time. Data collected regarding the recipient in the peri-transplant period included age, gender, indication for transplant, technique of transplant, and use of cardiopulmonary bypass (CPB).

2.1. Donor and recipient surgery

We used well-established criteria for accepting donor lungs including objective evidence of adequate gas exchange and bronchoscopic evaluation to exclude aspiration or purulent secretions [5]. Standardized organ procurement and recipient implantation techniques were utilized for lung transplantation. A cold crystalloid preservation solution (LPD or EC) was infused via the donor pulmonary artery at low pressure in an antegrade fashion immediately following prostaglandine intrapulmonary artery injection. During the procurement, the vascular structures were divided in situ and the trachea was dissected well proximal to the carina. With the lungs partially inflated, the trachea was divided between staple lines and the organ transported to the center immersed in either EC or LPD. The most common recipient operation performed was a single lung transplant accessed through a posterolateral thoracotomy. Double lung transplantation was performed using a sequential single lung implantation technique through bilateral anterolateral thoracotomies either with or without transverse incision of the sternum. Rarely, bilateral posterolateral thoracotomies were indicated for sequential single lung transplantation when mediastinal shifting led to difficult exposure of lung.
hilum structures requiring turning and re-draping the patient.

The need for CPB was determined based on trial occlusion of the pulmonary artery with one lung ventilation as indicated by pulmonary pressures changes, intolerance of single lung ventilation, or increasing hemodynamic instability. Once the donor lung was present in the operating room, the recipient pneumonectomy was completed. The bronchial anastomosis was accomplished first, generally followed by the vascular pulmonary artery and left atrial cuff anastomoses. De-airing was done thoroughly through the atrial cuff anastomosis.

2.2. Statistics

Statistical analysis was conducted using analysis of variance (ANOVA) and followed by unpaired Student’s t-test to determine significant differences between groups. Categorical data were analyzed by chi-square tests. Results are expressed as mean ± standard error. Significant differences are reported for p-values less than 0.05.

3. Results

The mean age of the 112 retrospectively analyzed patients, who underwent lung transplantation between 1997 and 2000, was 53.5 ± 8 years and 62% of them were male. Of these, 72 patients (64%) received single lung transplantation and 40 patients (36%) had sequential bilateral lung transplantation for various end-stage lung diseases. The majority (64%) of these patients had chronic obstructive lung disease and 26% had idiopathic pulmonary fibrosis. Cystic fibrosis was the indication for lung transplantation in 9% and miscellaneous disorders (lymphangiomomatosis, histiocytosis) were documented in 1% of the recipients. The donor age was 38.4 ± 9 years and the mean ischemic time of the donor lungs 231 ± 14 min. Cardiopulmonary bypass-supported lung transplantation was performed in 12% of the lung transplantation procedures. Invasive pulmonary artery pressure monitoring revealed systolic pulmonary artery pressures greater than 60 mmHg in 35% of the recipients. Using the ISHLT lung transplant injury grade III, defined by a FiO2/PaO2 ratio of less than 200 mmHg measured within the initial 48 h after transplantation, led to the identification of 20 patients (18%) with severe post-transplant ischemia—reperfusion injury and acute graft failure. Eight patients died within 90 days (mortality rate of 40%). Early ECMO was used in five patients. Three patients were successfully weaned off ECMO support.

A correlating donor characteristic was age greater than 35 years (45%, p = 0.01). The mode of donor brain death was difficult to assess mainly due to incomplete donor records. Even by categorizing the causes of brain death into three groups (closed head injury, intracranial bleeding, and penetrating trauma), there was no significant relation. We also observed no correlations between the recipients’ lung diseases, ischemia—reperfusion injury, and operative techniques (single or sequential bilateral transplantation or cardiopulmonary bypass support, p > 0.35). Recipient intraoperative systolic pulmonary artery pressure greater than 60 mmHg (48%, p < 0.05) was significantly correlated with ischemia—reperfusion injury.

The mean age of the Apt-EC group was significantly higher (56.2 ± 7 years) than that of the control group and 66% in the group were male. In the Apt-EC group, 20 patients (58%) received single lung transplantation and 15 patients (42%) had sequential bilateral lung transplantation for COPD (51%), idiopathic pulmonary fibrosis (38%), cystic fibrosis (9%), and miscellaneous disorders (2%). The donor age (42.4 ± 12 years) and the mean ischemic time of the donor lungs (258 ± 36 min) were significantly higher than in the control group. Cardiopulmonary bypass was used for 9% of the lung transplant procedures. Invasive pulmonary artery pressure monitoring revealed systolic pulmonary artery pressures greater than 60 mmHg in 33% of the recipients, which was significantly different compared to the control group. Severe ischemia—reperfusion injury was observed in two patients (6%), one single and one sequential bilateral lung transplant recipient of the Apt-EC group, which was unrelated to donor age or recipient pulmonary artery pressure. There was no ischemia—reperfusion associated mortality.

The mean age of the lung recipients (52.5 ± 10 years) of the Apt-LPD group was comparable with the mean ages and underlying end-stage lung diseases (obstructive lung disease 42%, idiopathic pulmonary fibrosis 48%, cystic fibrosis 8%, and miscellaneous disorders 2%) of the previous groups. The 24 recipients (67% males, 59% single transplants) of the Apt-LPD group received 34 lung grafts implanted after significantly longer mean ischemic times (317 ± 85 min) and from markedly older donors (mean age 46.1 ± 12 years) compared to the other groups. Cardiopulmonary bypass was used for 12.5% of the lung transplant procedures and was not significantly different compared to the other groups. Invasive pulmonary artery pressure monitoring revealed systolic pulmonary artery pressures greater than 60 mmHg in 38% of the recipients, which was insignificantly different compared to the control group. Severe ischemia—reperfusion injury was observed in two patients (9%) affecting three lungs of the two recipients who underwent sequential bilateral lung transplantation. The right transplant lung of this patient with a past medical history of severe asthma and obstructive lung disease, which was implanted first, was more affected by X-ray and bronchoscopic evaluations (opacities, clear secretions solely from the right lung). This patient improved after catecholamine support, aggressive diuresis, and prone positioning. The second patient (idiopathic fibrosis, secondary pulmonary hypertension, systolic pulmonary artery pressure 90 mmHg, right heart dysfunction) with severe ischemia—reperfusion injury developed graft failure and required immediate ECMO support. This patient died on postoperative day 10 due to therapy-resistant coagulopathy, right heart failure, and intracranial bleeding. The ischemia—reperfusion-related mortality rate was 50% unrelated to donor or recipient characteristics. One patient had a severely decreased P/F ratio of 115 mmHg and diffusely increased densities on chest X-rays following sequential bilateral lung transplantation for cystic fibrosis. Bilateral hemotoraces were found on re-exploration and treated. Table 1 summarizes donor and recipient characteristics of the three lung transplantation groups.
Primary graft dysfunction. They proposed severity grading on chest X-rays. In 2004, an International Society for Heart increased pulmonary vascular permeability, and infiltrates to describe poor pulmonary function following lung trans- reperfusion injury. By itself, or the ischemic times could not be attributed to the recipient. The use of cardiopulmonary bypass, the procedure for grade II patients the ray. For grade II patients the SPAP: systolic pulmonary artery pressure.

<table>
<thead>
<tr>
<th>Table 1 Donor and recipient characteristics</th>
<th>Control transplants (n = 112)</th>
<th>Apt-EC group (n = 35)</th>
<th>Apt-LPD group (n = 24)</th>
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<tr>
<td>Emphysema (%)</td>
<td>64</td>
<td>51</td>
<td>42</td>
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<tr>
<td>Fibrotic lung disease (%)</td>
<td>26</td>
<td>38</td>
<td>48</td>
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<tr>
<td>Cystic fibrosis (%)</td>
<td>9</td>
<td>9</td>
<td>8</td>
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<tr>
<td>Miscellaneous (%)</td>
<td>1</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Donor age (years)</td>
<td>38.4 ± 9</td>
<td>42.4 ± 12</td>
<td>46.1 ± 12</td>
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<tr>
<td>Recipient age (years)</td>
<td>53.5 ± 8</td>
<td>56.2 ± 7</td>
<td>52.3 ± 10</td>
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<td>SPAP &gt; 60 mmHg (%)</td>
<td>38</td>
<td>35</td>
<td>38</td>
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<tr>
<td>Ischemic time (minutes)</td>
<td>231 ± 14</td>
<td>258 ± 36</td>
<td>317 ± 85</td>
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<td>Single lung transplant (%)</td>
<td>64</td>
<td>58</td>
<td>59</td>
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<tr>
<td>Double lung transplant (%)</td>
<td>36</td>
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<tr>
<td>Severe reperfusion injury (%)</td>
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<td>6</td>
<td>9</td>
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<td>Reperfusion injury mortality (%)</td>
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4. Discussion

Despite refinements in lung preservation and improvements in surgical techniques and perioperative intensive care management, ischemia—reperfusion injury remains a significant cause of early graft failure, morbidity, and mortality following lung transplantation. Of all lung transplants, 57—97% showed some degree of perihilar infiltrates or reperfusion edema on chest X-ray examinations after implantation [6]. Approximately 20—40% of lung transplant recipients will experience a clinically significant degree of reperfusion injury, which could have associated mortality rates of 20—57% [6,7]. These published findings are comparable with the results of this study. In the control arm of this investigation, 18% of the transplanted patients developed severe ischemia—reperfusion injury and graft failure, associated with a mortality rate of 40%. In 25% of these patients, primary graft failure required ECMO support. The significant factors correlating with reperfusion injury were older donor age and markedly increased pulmonary artery pressure in the recipient. The use of cardiopulmonary bypass, the procedure by itself, or the ischemic times could not be attributed to the occurrence of reperfusion injury.

Ischemia—reperfusion injury-associated primary graft dysfunction is one of many terms, which have been used to describe poor pulmonary function following lung transplantation. The syndrome is characterized by hypoxia, increased pulmonary vascular permeability, and infiltrates on chest X-rays. In 2004, an International Society for Heart and Lung Transplant working group developed definitions of primary graft dysfunction. They proposed severity grading from I to III, which is based on the ratio of arterial PO2 to the FIO2 and measured within the initial 48 h following lung transplantation. Grade I patients have infiltrates on chest X-ray. For grade II patients the P/F ratio falls between 200 and 300. For grade III, the least favorable grade, the ratio is less than 200. For the purpose of this study, solely grade III was applied. Chest X-ray studies were not consistently available and therefore, these data were not incorporated into the analysis. King et al. [7] used the same P/F ratio as a mode to evaluate patients for ischemia—reperfusion injury after lung transplantation. They could demonstrate a significantly greater mortality rate, longer intensive care unit and hospital stay in lung transplant patients with a P/F ratio below 200 compared with patients with a ratio above 200. Primary graft failure caused by ischemia—reperfusion injury is the final result of a series of negative effects occurring from the event of donor brain death to the time of graft perfusion after implantation. The deleterious effects of brain death on donor organ function have been described thoroughly over the last few years. Profound interruptions of homeostatic regulations and endocrine function and an intense inflammatory reaction may reduce the tolerance of the organs to handle a period of ischemia and cold preservation [8,9]. Over the past few years, strategies were installed to help prevent preservation-related lung transplant dysfunction. In very high-risk patients—for example in recipients with pulmonary hypertension—the extended use of ECMO intraoperatively and postoperatively might show protective effects in avoiding transplant organ edema since it allows controlled reperfusion of the lung grafts and hemodynamic support. Other methods such as slow pulmonary artery clamp release in order to control the flow through the lung grafts are still under investigation. Transplant surgeons of these institutions do not apply this technique.

Currently, many lung transplant centers, which used Euro-Collins (EC) flush solutions or fewer, which used University of Wisconsin solution as their standard single flush pulmonary artery intracellular-based potassium-rich infusion, switched to an extracellular low potassium dextran (LPD) solution. LPD single flush solution was also used for the last 34 lungs procured and transplanted into 24 patients of this study. There is considerable evidence from laboratory studies that LPD provides excellent lung preservation for up to 24 h and limits the extent of ischemic—reperfusion injury, especially when compared to EC [10,11]. Many clinical studies attempted to show a reduction in the occurrence of postlung transplant graft failure. However, these studies were limited in terms of small numbers of enrolled patients, unmatched cohorts, and the use of controls from a different transplantation era. One specific study addressed many of these concerns and failed to demonstrate a significant difference between LPD and EC in clinical lung preservation [12].

The two centers of this study adopted the LPD preservation protocol given its uncomplicated de-airing process through the left atrial cuff anastomosis and because a low
potassium solution does not generally induce malignant arrhythmias, which can be observed with potassium-rich intracellular-type preservation solutions.

The discovery of key cellular events mediating the phenomenon of ischemia—reperfusion injury has been an important goal of lung transplantation research in the past few years. It is now widely accepted that lung transplant ischemia—reperfusion injury involves pulmonary macrophages and circulating leukocytes in a biphasic response [13]. The early phase is mediated by donor pulmonary macrophages and is followed by a late injury induced by recipient circulating leukocytes. The specific reperfusion component of the injury cascade is mediated in a large part by neutrophil—endothelial adherence and subsequent extravasation into tissues causing neutrophil-mediated organ injury [14,15]. In fact, when the neutrophils are activated by adherence to the endothelial tissue, they secrete reactive oxygen species and proteolytic enzymes. The final response is the release of inflammatory substances and interleukins. Interleukin (IL) -8 seems to be upregulated and high levels were found to correlate with the incidence of primary graft failure after reperfusion [16]. A possible mechanism by which reperfusion injury develops in these patients is through mechanical disruption of the pulmonary vascular endothelium, production of interleukin-8, and platelet-activating factor [17]. This results in profound structural and functional breakdown of delicate lung parenchyma causing capillary leaks with subsequent interstitial fluid accumulation leading to increased pulmonary edema, lung transplant dysfunction, and finally the systemic inflammatory response syndrome (SIRS).

An agent that may combat this process is much sought after in lung transplantation research. For this reason, aprotinin, a serine-protease inhibitor that is in wide clinical use in cardiovascular surgery, may be ideally suited to reduce the effects of lung reperfusion injury [18,19]. Asmiakopoulos et al. [15] demonstrated thoroughly in vivo and in vitro that aprotinin inhibits neutrophil extravasation and secretion of myeloperoxidase from neutrophils. In addition to the attenuation of neutrophil activation, aprotinin decreased IL-8 concentration and leukocyte adhesion molecule expression [20,21].

By adding aprotinin to organ preservation solution lung reperfusion-injury decreased experimentally [2]. It also significantly improved pulmonary function during reperfusion in an isolated, whole-blood perfused rabbit lung model [22]. Adding aprotinin to LPD single flush pulmonary solution in an in situ normothermic ischemic lung model prevented lung ischemia—reperfusion injury and maintained the morphological, functional, and biochemical integrity of the lungs [23]. The Groningen Lung Transplant Group showed that the administration of aprotinin is safe, and that clotting and fibrinolytic disturbances were reduced in clinical lung transplantation [24]. In the present study, the high-dose regimen of aprotinin (2 million KIU loading dose, 500,000 KIU/h during surgery, 2 million KIU supplemented to the pump prime when cardiopulmonary bypass was used) was applied in 59 patients who underwent single and bilateral sequential lung transplantation for similar end-stage lung disease as the 112 patients of the control group without aprotinin. A significant reduction of ischemia—reperfusion injury and primary graft failure was observed in the aprotinin-treated lung transplant patients, which resulted in a markedly decreased mortality rate. Adverse effects were not documented in association with aprotinin administration. They are unlikely to occur since all lung recipients are treated pre-operatively with high doses of steroids.

In 24 of the 59 lung transplant patients managed with aprotinin, LPD single pulmonary artery flush solution was administered as described by Strueber et al. [11]. There were no beneficial effects observed since the already very low incidence rate of ischemia—reperfusion injury was not further decreased. Whereas the aprotinin-LPD flush solution group was lower in numbers and the statistical power therefore diminished, the lung transplantations in this group were of higher risk from the beginning due to older donor organs, higher pulmonary artery recipient pressures, and significantly longer ischemic times.

The potentially positive effects of aprotinin on ICU length of stay, mechanical ventilation times, reduction of blood loss, and overall costs were not investigated and were not the subject of this bi-institutional study since different lung transplant management protocols were applied making a comparison difficult.

In summary, adding aprotinin to the routinely used single pulmonary artery crystalloid flush solutions and using high-dose aprotinin protocols in clinical lung transplantation led to a significantly reduced incidence of ischemia—reperfusion injury and primary graft failure associated with a decreased mortality rate in clinical lung transplantation.

References

control group were managed with Euro-Collins solution. Many with LPD? Aprotinin, how many of these lungs were preserved with Euro-Collins and how many with LPD?

Dr Bittner: This is correct, the historical control group of 112 patients was managed with Euro-Collins solution only and compared to the group of 35 patients receiving 59 lungs who had Euro-Collins with aprotinin and a similar third group of lung transplant patients managed with Perfadex and aprotinin.

Dr Van Raemdonck: But the numbers are small in one group.

Dr Bittner: I agree. That is the reason why I did not perform a correlation analysis. The Perfadex group is a little bit short of power to demonstrate a mortality impact, however, powerful enough to show a significant decrease in the occurrence of reperfusion injury.

Dr N. Yonan (Manchester, UK): Well, we all know that the causes of reperfusion injury are multifactorial. There are donor factors; there are ischaemic time issues; controlled reperfusion at the time of surgery; the use of bypass, which obviously improves controlled reperfusion; and the use of nitric oxide, whether it's early or in the ICU. I'm not sure if you have looked at all these factors. I think they are directly relevant to reperfusion. As my colleague said, it is happily getting less common since we got away from Euro-Collins solution. I didn't see a correlation with ischaemic time and, for example, controlled reperfusion. Do you ever use controlled reperfusion?

Dr Bittner: I use controlled reperfusion, not in these patients presented here, but I do that in patients with Eisenmenger's, heart–lung transplant, or with patients with primary pulmonary hypertension, and I control the reperfusion by using ECMO. I do these procedures on ECMO, allowing me to control the reperfusion. It does have excellent results. I leave the ECMO in and I explant the ECMO 2 days later semielectively in the intensive care unit. I agree absolutely. However, I want to say that these patients that I just presented were a cluster out of 455 patients. I presented those because they were all comparable in their management preoperatively, postoperatively, and if I go back to the results of this study, we just started a randomized prospective aprotinin trial having enrolled 20–25 patients so far.

Dr Yonan: Just one point. Most of us use aprotinin at recipient surgery, particularly if you use bypass. I'm not sure how that affects your conclusion. Do you use aprotinin in recipients at all?

Dr Bittner: Yes, I do. I apply the Hammersmith protocol, as it comes with the most experience out of your country. I use it in the exact way in all the recipients. I'm using my flush, procuring the lungs, and I start the Hammersmith protocol of aprotinin at the recipient site: test dose, loading dose of 2 million KIU, followed by continuous perfusion.

Dr S. Aharinejad (Vienna, Austria): Let us assume for a second that we had a measure preoperatively as a risk factor to identify recipients at risk for PGD, primary graft dysfunction. What would you do then if we had this measure to identify those patients who could develop PGD? I'm not saying we have it.

Dr Bittner: What would I change in my management? Certainly they still would get aprotinin, and I certainly would probably look into what the other speaker, Nizar A. Yonan, just mentioned such as controlled reperfusion.