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 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 peripherally managed with aprotinin, a serine-proteinase inhibitor (TrasyloI; Bayer Pharmaceuticals, West Haven, CT, USA). Thirty patients were excluded from the data analysis because of clinical incomparability 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, Vitroliffe, 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/F ratio within 48 h post-transplant was less than 200 with F being the fraction of inspired oxygen, and P 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 peritransplant 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.

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 (lymphangiomymatosis, 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 postoperative day 10 due to therapy-resistant coagulopathy, right heart dysfunction, and prone positioning. The second patient (idiopathic fibrosis, second-year pulmonary hypertension, cystic 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 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-EC 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, cystic 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 hemithoraces were found on re-exploration and treated. Table 1 summarizes donor and recipient characteristics of the three lung transplantation groups.
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18% of the transplanted patients developed severe ischemia—
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spiration protocol given its uncomplicated de-airing process
through the left atrial cuff anastomosis and because a low
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 trans-
plant 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

4. Discussion

Despite refinements in lung preservation and improvements in surgical techniques and perioperative intensive care management, ischemia—reperfusion injury remains a sig-
ificant cause of early graft failure, morbidity, and mortality following lung transplantation. Of all lung transplants, 57—
97% showed some degree of perihilar infiltrates or reperfu-
sion 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 trans-
plantation. 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

<table>
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<tr>
<th>Table 1 Donor and recipient characteristics</th>
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<tr>
<td>Control transplants (n = 112)</td>
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<tr>
<td>Emphysema (%)</td>
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<tr>
<td>Fibrotic lung disease (%)</td>
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<td>Cystic fibrosis (%)</td>
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<td>Miscellaneous (%)</td>
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<td>Donor age (years)</td>
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<td>Recipient age (years)</td>
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<tr>
<td>SPAP &gt; 60 mmHg (%)</td>
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<tr>
<td>Ischemic time (minutes)</td>
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<td>Single lung transplant (%)</td>
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<tr>
<td>Double lung transplant (%)</td>
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<tr>
<td>Cardiopulmonary bypass (%)</td>
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<tr>
<td>Severe reperfusion injury (%)</td>
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<td>Reperfusion injury mortality (%)</td>
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SPAP: systolic pulmonary artery pressure.
* Significant difference in comparison with the control group.
apotinin. A significant reduction of ischemia—reperfusion disease as the 112 patients of the control group without sequential lung transplantation for similar end-stage lung was applied in 59 patients who underwent single and bilateral 500,000 KIU/h during surgery, 2 million KIU supplemented regimen of aprotinin (2 million KIU loading dose, 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 save, 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 crystallloid 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. If it is an advance? Ann Thorac Surg 2003;75(3):990–5.


Appendix A. Conference discussion

**Dr D. Van Raemdonck** (Leuven, Belgium): I may have missed it from your presentation, but can you tell us in the control group, the group without aprotinin, how many of these lungs were preserved with Euro-Collins and how many with LPD?

**Dr Bittner**: All the procured lung grafts of the entire 112 patients of the control group were managed with Euro-Collins solution.

**Dr Van Raemdonck**: So actually you are comparing a group with Euro-Collins only versus two other groups, and we know that since the introduction of the LPD solution, the incidence of reperfusion injury has decreased significantly.

**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 into the remaining 300 patients, then I can also look into aspects of nitric oxide used early, late; however, I do not reach any power here at all since the patients are poorly comparable. I would like to emphasize on comparable groups of patients we all see in lung transplantation — IPF, COPD, cystic fibrosis. I call them a rather low-risk group, and even with those we see reperfusion injury. I have shown and documented that it is statistically concerning that adding of aprotinin did show beneficial effects. Based on 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.