Replacing cardiopulmonary bypass with extracorporeal membrane oxygenation in lung transplantation operations

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Abstract

Objective: Cardiopulmonary bypass (CPB) support is required in some lung transplantation (LTX) operations. CPB support and full-dose heparin increases the risks of bleeding and early graft dysfunction. We report our experiences of replacing CPB with heparin-bonded low-dose heparin extracorporeal membrane oxygenation (ECMO) support in LTX surgery. Methods: From 2003 to 2005 forty-seven patients were transplanted. Thirty-seven LTX patients were retrospectively evaluated for this study (10 patients were excluded due to heart-lung-, lung-kidney transplantation, LTX with bypass grafting, and ASD closure or emergency CPB support). Extracorporeal circulation support was necessary in 40% of the 37 LTX patients due to severe primary or secondary pulmonary hypertension (P or SPHTN), right heart dysfunction, or hemodynamic instability. There were seven LTX procedures with CPB and eight implantations with ECMO support. CPB (high-dose heparin) and ECMO support (ACT 160—220 s) was always set up through femoral veno-arterial canulation. All patients had limited access thoracotomies without transsection of the sternum. Normothermia was maintained in all patients. CPB patients: PPH 15%, COPD 15%, IPF with mean PAP > 40 mmHg 70%. ECMO patients: PPH 13%, COPD 13%, IPF with severe PAP pressure elevation 74%. Results: In patients undergoing LTX for PPH, the ECMO support was directly extended into the post-operative period. Packed red blood cell (PRBC) transfusion requirements during the operation and the first 24 h were 13.25 ± 1.6 PRBC units versus 5.1 ± 2.8 PRBC units on CPB (p = 0.02). Operative time was longer (p = 0.11) in the ECMO LTX (451 min ± 76 vs 346 ± 140). The increased 90-day mortality rate of the ECMO patients showed a trend toward significance (p = 0.056), which was related to infectious complications (3 vs 1 patient). Severe graft ischemia/reperfusion injury occurred in 9% in the CPB versus 13% in the ECMO group. The 1-year survival was significantly reduced in ECMO patients (p = 0.004, log-rank test). Conclusions: The advantages of femoral canulation rather than conventional central connections in lung transplantation procedures led to an undisturbed operative field. A significantly higher blood product amount was required in ECMO patients, which might lead to increased infection and mortality rates. CPB, obviously, should remain the standard support technique if extracorporeal circulation is required in lung transplantation surgery.

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1. Introduction

Lung transplantation has become the standard of care for most causes of end-stage lung disease [1] and is an 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 use of extracorporeal circulation and cardiopulmonary bypass (CPB) is required for oxygenation and hemodynamic support in thoracic transplant procedures like heart and heart-lung transplantation. CPB support has also been applied in lung transplantation but its requirement is not always necessary because of improved single lung ventilation techniques and hemodynamic support options. The use of extracorporeal circulatory support techniques for lung transplantation surgery depends primarily on the functional status of the right heart, severity of pulmonary hypertension, and the tolerance of isolated lung ventilation [2]. Furthermore, the lung transplantation unit specific preferences for the use of circulatory support techniques play an important role [3]. In patients with elevated pulmonary artery pressure, the lung transplantation operation is usually performed with CPB support, which allows optimal intra-operative hemodynamic stability and avoids the initial overflow of the first implanted lung [3,4].

The use of CPB, however, can lead to early graft dysfunction and bleeding-associated complications due to the required full systemic heparin administration and the activation of inflammatory mediators [5,6]. Extracorporeal membrane oxygenation (ECMO) support is an alternative...
technique of extracorporeal circulation, which has already been used during the initial stage of lung transplantation [7]. ECMO has the capacity to support gas exchange and hemodynamics without the need for high-dose heparin administration and anticoagulation therapy. Its prolonged use and positive impact on outcomes following graft failure after lung transplantation is well documented [8].

This study was designed to investigate the efficacy and safety of the intra-operative use of ECMO in patients undergoing lung transplantation surgery for various end-stage lung diseases compared with standard CPB support techniques.

2. Patients and methods

The prospectively collected data of a newly established lung transplant center were analyzed. Forty-seven patients were transplanted by the same surgical team from 2003 until the end of 2005. Extracorporeal support was required in 25 of the lung transplantation procedures (LTX). The technique of extracorporeal support (ECS) used was CPB or ECMO. Subject of this retrospective study were 15 patients with similar end-stage lung disease (2 females, 51 ± 8 years of age) who required electively the use of CPB (7 patients) or ECMO (8 patients) for intra-operative lung transplantation support. The use of CPB or ECMO for lung transplantation surgery was arranged through identical femoral vessel cannulation techniques (see below). Fig. 1 summarizes the characteristics of the study patients. Excluded from the study were eight patients who underwent lung transplantation in combination with cardiac surgery and CPB (PFO closure, coronary artery bypass grafting, tricuspid valve repair) or additional procedures such as kidney transplantation under ECMO support. Further two patients were excluded from the analysis due to different surgical techniques used. One patient underwent heart-lung transplantation and the other underwent emergency CPB connection through ascending aorta and right atrium cannulation.

All transplant patients received the same standard immunosuppressive protocol, which was a triple medication regimen consisting of glucocorticoids, cyclosporine, and mycophenolate mofetil. The immunosuppressive medications were started 4–6 h preoperatively in all recipients. Additionally, all patients were managed with the same high-dose aprotinin protocol. Aprotinin was administered by means of a central venous line according to the following regimen: following a test dose of aprotinin, the loading dose of 280 mg aprotinin or 2 million (2,000,000) kallikrein inhibiting units (KIU) was infused, followed by 500,000 KIU/h 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.

2.1. Extracorporeal circulatory support devices

The ECMO heparin-bonded circuit used was the D905 EOS ECMO hollow fiber membrane oxygenator (COBE, Cardiovascular, Anvada, CO, USA), 1.2 m² membrane surface area, priming volume 300 ml, and heat exchange surface area 0.14 m² allowing maximal blood flow of 5000 ml/min through heparin-bonded tubing and cannula system.

The CPB system used was the MEDOS HLT 8000 heart-lung machine series (MEDOS, Stolberg, Germany) in combination with Stöckert’s third-generation perfusion system consisting of a hardshell venous reservoir (4000 ml), heparin-coated hollow fiber oxygenator (surface area 1.9 m²), heat exchanger (0.45 m²), priming volume 1200 ml, and cardiotomy section allowing blood flow rates of 1–7 l/min. The Medtronic Carmeda heparin-bonded tubing circuit (Medtronic Cardiopulmonary, Anaheim, CA) was used for both circulatory support systems. Heparin infusion was titrated to maintain an activated clotting time (ACT) of >450 s for CPB supported lung transplant operations and 160–220 s for the ECMO supported procedures. CPB and ECMO flows were 2.0 to 2.4 l/min/m². Packed red blood cell (PRBC) transfusion was performed when the hemacrit dropped below 30%. Normothermia was maintained in all patients.

2.2. 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 [9]. Standardized organ procurement and recipient implantation techniques were utilized for lung transplantation (cold crystalloid preservation solution of low-potassium dextan solution or LPD, Vitrolife, Gottenberg, Sweden) 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 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 was immersed in LPD.

A pulmonary artery catheter was inserted through the right neck to monitor continuously the right arterial and pulmonary artery pressure and a double-lumen endo-
tracheal tube was placed allowing isolated lung ventilation. Double lung transplantation was performed using a sequential single lung implantation technique either through bilateral anterolateral thoracotomies 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 (one patient). Single lung transplantation was performed through a serratus muscle-sparing posterolateral thoracotomy.

Once the donor lung was present in the operating room, the recipient pneumonectomy was completed. The bronchial anastomosis was accomplished first and was generally followed by the vascular pulmonary artery and left atrial cuff anastomoses. De-airing was done thoroughly through the atrial cuff anastomosis.

In all patients of this study, ECMO and CPB support was set up through the femoral veno-arterial vessels. Monofilament 5-0 purse string sutures were applied to the anterior wall of the femoral artery and vein. The Seldinger cannulation technique was used to introduce minimal-invasive cardiac surgery heparin-bonded venous (usually 22 Fr) and arterial cannulas (18 Fr). In case of small arterial diameter and complete occlusion of the vessel by the arterial cannula, a separate arterial cannulation (10 Fr) of the distal limb was performed.

2.3. Data analysis

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. The association between risk factors and mortality was first analyzed with Fisher’s exact test. A logistic multivariate regression model was then used to examine synergistic effects of potential predictors (massive blood product transfusions of greater than 8 units of packed red blood cells, ECMO use, CPB use, survival). The statistical analysis was performed using SPSS 12.0 and Microsoft Excel. Results are expressed as means ± the standard errors. Significant differences are reported as exact p-values.

3. Results

There were no differences in the surgical implantation technique and the underlying end-stage lung diseases between the CPB and ECMO supported lung transplantation procedures. There were seven sequential bilateral and one single lung transplantation procedures in the ECMO group and six sequential bilateral and one single lung transplantation operations in the CPB group. All surgical procedures were performed through limited-access muscle and sternum sparing bilateral anterolateral or posterolateral thoracotomies. The mean cold and warm ischemic times were similar between the CPB group (335 ± 79 min and 54 ± 13 min) and ECMO group (343 ± 73 min and 57 ± 15 min). Operative time was longer (p = 0.11) in the ECMO group (451 ± 76 min) versus 346 ± 140 min in the CPB group.

ECMO group, severely elevated pulmonary artery pressure (systolic PAP > 90 mmHg) was diagnosed. In these patients, ECMO was extended into the post-operative ICU period. Lower extremity perfusion was established through a 10 Fr femoral artery cannula insertion. ECMO support was successfully post-operatively weaned within the initial 12 h and explanted on the ICU. Overall, there were no complications directly related to ECMO or CPB support. Weaning from mechanical ventilation and subsequent extubation times were significantly shorter in the CPB-supported patients: 3.9 ± 3.7 days versus 10.8 ± 6.6 days (ECMO, p = 0.03).

Using the ISHLT lung transplant injury grade III, defined by a FiO2/PaO2 ratio of less than 200 mmHg was measured within the initial 48 h after transplantation, led to the identification of one patient in the CPB group and one patient in the ECMO group with severe post-transplant ischemia—reperfusion injury. Following bronchoscopy, chest-X-ray, and chest computed tomography examinations the patients were taken back to the operating room. The previously ECMO-supported patient improved following evacuation of large chest cavity hematomas, which compromised transplant lung inflation and expansion. A thorough inspection did not reveal surgical bleeding sites. The CPB supported 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 and massive blood product transfusions. This patient died on post-operative day 10 due to therapy-resistant coagulopathy, right heart failure, and intracranial bleeding. In this patient several re-explorations and thoracotomies for bleeding were performed; however, an obvious surgical bleeding site was never identified.

The requirement for blood product administration (packed red blood cell) was significantly different between both groups during the operation and over the first 72 h. Their average transfusion requirements were 13.25 ± 1.6 PRBC units in the ECMO supported patients versus 5.7 ± 2.8 PRBC units in the CPB-supported lung transplantation patients (p = 0.02). For comparison, the patients undergoing lung transplantation without extracorporeal support required 2.7 ± 0.9 PRBC units over the first 72 h (p < 0.001). Multivariate regression analysis revealed that eight and more PRBC units transfused within the early post-operative period reached near significance for mortality prediction in combination with the use of ECMO (p = 0.06, 95% confidence interval 9.57—16.93).

**Table 1**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CPB</th>
<th>ECMO</th>
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<tbody>
<tr>
<td>Ischemia (min)</td>
<td>335 ± 79</td>
<td>343 ± 73</td>
</tr>
<tr>
<td>Warm ischemia (min)</td>
<td>54 ± 13</td>
<td>57 ± 15</td>
</tr>
<tr>
<td>Operative time (min)</td>
<td>345 ± 140</td>
<td>451 ± 76</td>
</tr>
<tr>
<td>Mechanical ventilation (days)</td>
<td>3.9 ± 3.7</td>
<td>10.8 ± 6.6</td>
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<tr>
<td>Packed red blood cells (units)</td>
<td>5.7 ± 2.8</td>
<td>13.25 ± 6.6</td>
</tr>
<tr>
<td>90-day mortality</td>
<td>1</td>
<td>3</td>
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(CPB: cardiopulmonary bypass, ECMO: extracorporeal membrane oxygenation). Differences in mechanical ventilation times and blood product transfusions were significantly different between the CPB and ECMO support techniques (p = 0.03, p = 0.02).
Three of the ECMO and one additional patient of the CPB-supported group died within 90 days of the lung transplantation procedure due to infectious complications. Three patients developed severe CMV and HSV viral sepsis (all recipients were CMV Ig-positive and one donor was CMV Ig-negative) and one patient expired of lung transplant bacterial pneumonia (Klebsiella pneumoniae, Pseudomonas aeruginosa) induced graft failure and intracranial hemorrhage under delayed ECMO support. The 1-year survival rate was reduced ($p = 0.004$, log-rank test) in the ECMO-supported patients. Table 1 summarizes the important findings.

4. Discussion

The majority of single and sequential bilateral lung transplantation surgery is performed without extracorporeal circulatory support (CPB or ECMO) on a routine basis for a wide variety of end-stage lung disorders with steadily improving 5-year morbidity and mortality rates. The use of CPB has decreased dramatically since the early days of lung transplantation. Our preference is to avoid CPB, whenever possible, and thus, avoiding the CPB-associated complications of coagulopathy and bleeding, neurological and renal dysfunction. Hemodynamic instability, the inability to sufficiently oxygenate with one lung ventilation, dramatic increases in pulmonary artery pressure with pulmonary artery clamping and deterioration of right ventricular function require the employment of CPB. We, and others, prefer CPB support in lung transplantation surgery when the indication for lung transplantation is accompanied by severely elevated pulmonary artery pressures associated with right heart dysfunction [3,10,11]. The majority of these patients present either with primary pulmonary hypertension or idiopathic pulmonary fibrosis with secondary severely increased pulmonary artery pressures. These are the highest-risk patients in lung transplantation surgery. The majority of patients in this study presented with markedly increased pulmonary artery pressures and the lung transplantation surgery required CPB support. The use of CPB can further lead to increased blood product transfusions, increasing the release of cytokines, and activation of the systemic inflammatory response syndrome [6,12]. Its sequelae of reperfusion injury and early graft dysfunction in clinical lung transplantation are well described in association with CPB-supported surgery [13]. The administration of aprotinin decreased the incidence of severe ischemia–reperfusion injury in clinical lung transplantation [14]; however, the administration of blood products could not be avoided. A comparison of peri-operative blood transfusion requirements between double lung transplantation with and without CPB support by Gammie et al. [5] showed that the CPB group required significantly more blood transfusions (11.4 vs 6.0 units). The CPB-supported lung transplantation group of the present study had required markedly less packed red blood cell units (5.7 units) over 72 h. Interestingly, despite the avoidance of high-dose heparin administration due to the integration of heparin-coated tubing systems in the ECMO circuit of the ECMO-supported lung transplantation procedures, the transfusion of blood was significantly increased (mean of 13 units). The results of this study revealed that eight and more red blood cell units transfused within 72 h of lung transplantation in the combination with the use of intra-operative ECMO support, reached near significance for adverse outcomes following lung transplantation surgery. Transfusion-related lung injury is a thoroughly described phenomenon and clinically similar to the adult respiratory distress syndrome [15]. It has been linked to the transfusion of leukocyte antibodies in blood components. There are several potential mechanisms by which massive transfusion might predispose to direct lung transplant injury and impact on the immune system: cognate antigen–antibody interactions, activation of non-specific immunity through soluble mediators present in transfused blood, an increased risk of infection through transfusion-associated immunomodulation leading to infection and sepsis; and volume overload in the face of increased permeability of the alveolar capillary membrane [16]. These combinations of effects could have contributed to the observed increased rate of early post-transplant viral infection and sepsis, which was the cause of significant morbidity and mortality in three lung transplant patients. One explanation for the increased use of blood transfusions in the ECMO group of this study is the significantly reduced priming volume in a patient population which was already present in a therapeutically induced end-stage lung disease related dehydrated state. In order to maintain effective and adequate high ECMO flow intravascular volume repletion was required. This was performed with high-molecular weight components and blood products to prevent transcapillary leakage and interstitial edema formation. Like in many other lung transplant centers observed, a very liberal blood product administration policy is applied in our lung transplantation unit meaning 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 post-operative bleeding is observed. This protocol assists in the management of 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.

The use of extracorporeal membrane oxygenation became a last resort treatment option for lung transplantation patients after surgery who developed severe ischemia–reperfusion injury and graft failure following surgery [8]. Many lung transplant centers judged the elective employment of ECMO as justified if graft failure is related to the ischemia–reperfusion syndrome, which is associated with hypoxia, endothelial permeability increase, and dense pulmonary infiltrates formation [17]. Only limited reports exist, which describe the intra-operative use of ECMO for lung transplantation surgery. Ko et al. described their experience of intra-operative ECMO use in five patients with primary pulmonary hypertension. ECMO support was extended into the post-operative period. All lung transplant patients had an uneventful recovery with excellent graft function [18]. Bilateral lung transplantation with intra- and postoperatively prolonged ECMO support was used in 17 patients with primary pulmonary hypertension [4]. Controlled reperfusion prevented the occurrence of reperfusion...
injury when ECMO was extended into the ICU treatment interval. However, rethoracotomy for bleeding was required in 25% of the total ECMO population, although heparin-coated tubing sets were used and systemic administration of heparin was avoided. Of note, they report only two deaths despite the use of ECMO. Ko et al. [19] extended their experience of intra- and post-operative ECMO support to 10 single and 3 bilateral sequential lung transplantations for various causes of end-stage lung disease. It was concluded that ECMO rather than CPB should be used for lung transplantation surgery. Multiple blood transfusions were required for bleeding and to maintain the hematocrit above 30% (intra-operative 2–30 units, post-operative 0–9 units of packed red blood cells), which was comparable to the results of the present study.

In this study, the surgical approach was identical in the ECMO and CPB patients. In all patients a limited access muscle- and sternum-sparing thoracotomy were performed and thorascopic instruments used. The femoral arteries and veins were cannulated for both techniques utilizing cannulas as frequently used in minimal invasive heart valve surgery. This provides an undisturbed and unobstructed surgical field at the lung hilum structures. Both support techniques maintained a high level of oxygenation and oxygen saturation throughout the operations. However, CPB achieved better hemodynamic support, allowed greater flow rates, and was independent of frequent fluid supplementation. One major advantage was the implementation of cardiotomy suction in all CPB-supported procedures, which allows the immediate return of the lost fully heparinized chest cavity blood and the establishment of a blood-less field. The results of this study show that high-dose heparinization was not associated with increased blood loss in CPB-supported lung transplantation operations. The major advantages of CPB support became obvious when very adipose patients and patients with large BSA presented with narrow chest cavities (as it is in idiopathic pulmonary fibrosis) and right heart hypertrophy and dilatation (patients with primary or secondary pulmonary hypertension). In these patients the lung hilum structure exposition for precise lung transplantation surgery required aggressive heart manipulations, pushing, lifting, and shifting. This was readily achieved in the CPB supported operations due to stable and higher CPB flow rates and maximum venous drainage capabilities leading to an empty-beating heart status with improved intrathoracic views. If there is need for extension of extracorporeal circulatory support into the post-operative period in CPB supported operations, the ECMO circuit could be connected to the already inserted femoral vessel cannulas with ease.

5. Limitations of the study

It is not a randomized prospective study of the intra-operative use of ECMO and CPB support. In general, randomized studies of different surgical techniques are difficult to arrange in lung transplantation surgery. The number of patients included in this study is low; however, it matches well with the number of patients discussed in the previous literature. The strengths of this study are that the two patient groups compared have similar characteristics and end-stage lung diseases in one of the first comparison studies of intra-operative use of CPB and ECMO in lung transplantation surgery.

In summary, extracorporeal circulatory support is required in certain lung transplantation operations. The ECMO supported lung transplant procedures required significantly more blood transfusions. The negative effects of multiple blood transfusions in the ECMO patients might have contributed to the extended ventilatory times, infectious complications, and mortality rates compared with the CPB supported lung transplantation operations. CPB remains the standard of support technique if extracorporeal circulatory support is indicated for lung transplantation surgery.

References


Appendix A. Conference discussion

Dr R.D. Davis (Durham, North Carolina, USA): I assume you were doing VA-ECMO for all these patients; is that correct?

Dr Bittner: That’s correct.

Dr Davis: Have you ever tried using VV-ECMO as a support in the patients who really don’t need hemodynamic support but rather oxygenation? We had excellent luck with doing that and it makes the anesthesia much easier and you can actually achieve the same thing without the femoral arterial complications that you tend to get as well as the systemic embolic phenomena.

And my other question that gets into this is the difference between your cardiopulmonary bypass group and your ECMO group in terms of blood utilization. Were you using some sort of scavenger circuit? And can you try to explain why you felt like you ended up with what appeared to be a much worse coagulopathy with the ECMO. It seems like you probably had a lot of blood loss and that you ended up giving defibrinated blood back in terms of using your BRAT circuit or whatever you’re using.

Dr Bittner: For the first question, yes, we have also tried and still use VV-ECMO support, but primarily in patients which present following the operation with graft failure which cannot be treated by less aggressive methods (turning the patient and frequent position changing, prone positioning). And the VV-ECMO can easily be performed in the intensive care unit, without going back to the operating room, with quite a success.

However, the VV-ECMO support does not support the hemodynamics, and some of these patients required intraoperatively additional hemodynamic support, which is often not sufficiently achieved through catecholamine administration. Subsequently, for additional hemodynamic support, I think, I believe, that VA ECMO support is necessary allowing you very higher flow rates.

Now, compare that to the cardiopulmonary bypass procedures — and here is the answer to your second question — in order to run ECMO efficiently in these patients who present, due to their end-stage lung disease majorly dehydrated, they require efficient flow rates of 4 l/min when hemodynamic instability occurs associated with a lot of volume administration. We hesitate to give crystalloids due to the capillary leak phenomena. We give blood liberally to allow for efficient ECMO runs. That is one of the reasons why the ECMO patients had more blood transfusions and a higher requirement of FFPs compared to the cardiopulmonary bypass group. Furthermore, the priming volume is 1200 ml, which also helps to run cardiopulmonary bypass efficiently because they get right away 1.2 l to support flow.

The use of the cardiotomy suction devices in the cardiopulmonary bypass group allowed the immediate return of chest cavity collected blood. In addition, the limited access lung transplant procedures can also lead to more fluid requirements due to the insignificantly longer operation times and the limited venous drainage and heart emptying in the ECMO patients. This can lead to difficult lung hilum exposure and frequent instability due to heart lifting and heart manipulations.

Dr W. Klepetko (Vienna, Austria): As you might have realized, your work is a bit opposite to what is our philosophy and what we reported yesterday. Now, the over all experience with ECMO cases you are presenting here is 10 or 11 patients. What we have seen in our series was a certain learning curve. Therefore, might it be due that there is as well a pronounced learning effect especially in the limited number of your patients.

Another question I would also like to raise is in regard to the blood loss you reported. Does this include intraoperative blood loss only or is the immediate postoperative period included?

Finally, we have identified the combination of induction therapy with ATG and the ECMO use as a problem especially for the function of the thrombocytes. Have you done the same observation?

Dr Bittner: To your first question in regards of learning curve, yes, since we just established our lung transplant program, there is an institutional learning curve which I cannot deny. I cannot compare the presentation of the data here to your great presentation of intra-operative ECMO use of your group yesterday because your study is a retrospective analysis, no comparison to CPB made, and the mix of patients you presented yesterday is not so prominent.

The third question was the immunosuppression and ATG in association with bleeding problems. As I stated, all patients had the same very aggressive immunosuppression protocol consisting of glucocorticoids, CNI, and CellCept.