

Institutional experience with extracorporeal membrane oxygenation in lung transplantation[☆]

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Abstract

Background: Extracorporeal membrane oxygenation (ECMO) is currently accepted in lung transplantation either to bridge patients to transplantation or to treat postoperatively arising severe primary graft failure. Based on promising initial experiences we have since 2001 implemented ECMO as the standard of intraoperative extracorporeal support in lung transplantation (LuTX) patients with haemodynamic or respiratory instability with the potential to prolong ECMO support into the perioperative period. The aim of this paper is to summarise our total experience with the use of ECMO in LuTX. **Methods:** We retrospectively reviewed all 306 patients undergoing primary lung transplantation from 1/2001 to 1/2006 with regard to the different forms of ECMO use. Results of all patients requiring ECMO were compared to those without ECMO during the observation period. **Results:** ECMO was used in 147 patients in total. Two patients were bridged to transplantation. A total of 130 patients received intraoperative ECMO support. In 51 of these patients ECMO was prolonged into the perioperative period. Five of these patients required ECMO support again in the postoperative period due to graft dysfunction. Contrary cardiopulmonary bypass was used in 27 patients mainly with concomitant cardiac defects. Eleven of these patients needed therapeutic ECMO in the further course. A total of 149 patients without relevant risk factors were transplanted without any intraoperative extracorporeal support. Six of these patients required ECMO support in the postoperative period for treatment of primary graft dysfunction. Overall 3-month, 1-year and 3-year survival rates were 88.6%, 82.1% and 74.63%. The mentioned survival rates were 85.4%, 74.2% and 67.6% in the intraoperative ± prolonged ECMO group; 93.5%, 91.9% and 86.5% in the no support group and 74.0%, 65.9% and 57.7% in the CPB group. **Conclusion:** ECMO is a valuable tool in lung transplantation providing the potential to bridge patients to transplantation, to replace CPB with at least equal results and to overcome severe postoperative complications. Favourable survival rates can be achieved despite the fact that ECMO is used in the more complex patient population undergoing lung transplantation as well as to overcome already established severe complications.

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Keywords: Lung transplantation; Extracorporeal membrane oxygenation; ECMO

1. Background

Extracorporeal membrane oxygenation (ECMO) is currently accepted in lung transplantation either to bridge patients to transplantation or to treat postoperatively arising severe primary graft failure. On the contrary cardiopulmonary bypass (CPB) remains the standard method in lung transplant recipients requiring intraoperative extracorporeal support. The intraoperative use of ECMO instead of CPB has so far been reported on a limited number of patients only by a Taiwanese group [1,2] and our own group [3]. Based on these initial experiences we have implemented ECMO as the standard of intraoperative extracorporeal support in lung

transplantation (LuTX) patients with haemodynamic or respiratory instability since 2001. This has led to a large experience with ECMO in the field of lung transplantation. The aim of this paper is to summarise this total experience.

2. Patients and methods

All patients undergoing primary lung transplantation from 1/2001 to 1/2006 were retrospectively analysed and divided into groups according to the different forms of ECMO application. Group I consisted of patients in whom preoperative ECMO was used to bridge patients on the waiting list. Group IIA included patients in whom ECMO replaced CPB during the operation if haemodynamic or respiratory support was required. In some of these patients ECMO was prolonged after the operation into the early postoperative period in order to provide prolonged reduced lung perfusion (group

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IIB). Group III consisted of patients who were operated on cardiopulmonary bypass either to allow concomitant correction of cardiac defects or if an extremely high blood turnover was anticipated due to previous operations and significant adhesions. Patients who were transplanted without any intraoperative support were stratified in group IV. Group V consisted of those patients where ECMO was applied at any time during the postoperative course for treatment of arising or established primary graft dysfunction (PGD). Results of all patients requiring ECMO were analysed and compared to those without ECMO during the observation period.

2.1. Lung transplantation technique

The operative technique for lung transplantation was standardised with all organs being harvested after flush perfusion with 6 l of low potassium dextrane solution (Perfadex®). Until 2004 antegrade flushing only was used. Thereafter we introduced a retrograde flush at the backtable after removing the lungs from the donor. Surgical approach was either a uni- or bilateral anterolateral thoracotomy in the 4th or 5th intercostal space or a bilateral thoracotomy with a transverse sternotomy (Clamshell incision). After a standard pneumonectomy and preparation of the hilum, the first step of the implantation was the bronchial anastomosis, which was performed in an end-to-end technique using a single running suture technique with 4/0 or 5/0 polydioxanone suture. Thereafter the atrial anastomosis was sutured using 4/0 prolene and the arterial anastomosis with 5/0 prolene. After retro- and antegrade flushing controlled reperfusion was performed. Double lung transplantation was performed in the sequential technique except for those cases performed on CPB where both recipient lungs were resected prior to implantation of the donor lungs. The technique for lobar and split lung transplantation in our department has been outlined before [4]. Suctioned blood was processed through a cell saver while the recipient bronchus was closed and was discarded as long as the recipient bronchus was open.

Basic immunosuppression consisted routinely of a triple drug regimen with either cyclosporine or tacrolimus, mycophenolate mofetil and corticosteroids. ATG induction therapy was routinely applied in CF and PPH patients. Other immunosuppression was used according to clinical necessity.

All patients routinely received antibiotic prophylaxis with piperacillin/tazobactam. Cystic fibrosis patients and patients with recurrent infections additionally received antibiotics according to resistance testing. In case of prolongation of ECMO beyond 48 h intravenous antifungal prophylaxis was added. Further treatment including rejection and infection monitoring by transbronchial biopsy and lavage was routinely performed according to standards.

2.2. ECMO management

The ECMO device consisted of the Medtronic Carmeda heparinbound system, a Medtronic Maxima hollow-fiber oxygenator, a Bio-Medicus BP-80 centrifugal pump, a flow probe and 3/8-in. internal diameter heparin-bound tubing. Because of the heparin-bound tubing sets, systemic administration of heparin was limited to an intravenous bolus of

75 IU/kg before cannulation. Human albumin (5%, 500 ml) with physiological saline (500 ml) supplemented with 1000 IU of heparin was used as priming solution. In case of prolonged use heparin was administered to adjust activated clotting time to 160–180 s. ECMO was routinely used in a veno-arterial fashion in order to combine the features of oxygenation and haemodynamical relief to the pulmonary circulation. Intraoperative monitoring of end-tidal CO₂ and pulmonary artery pressure are mandatory to correctly adjust ECMO flow. The patient was always kept normothermic.

In our initial experience ECMO was applied in all patients in the right groin, except for two children who were cannulated cervically. Insertion was performed after preparation of the vessels either in Seldinger technique or in an open fashion after clamping of the vessel. After placement of a cannulation suture the arterial cannula (15F–21F) was inserted in the common femoral artery. The diameter of the cannula was chosen after exploration of the femoral vessels in order not to compromise distal arterial flow. In the situation of a small femoral artery with significant obstruction by the cannula a small additional cannula connected by a Y-adapter was inserted for distal leg perfusion. The venous cannula was inserted in the common femoral vein (21F–28F) with the tip located close to the right atrium. Correct cannula position was verified by transesophageal echocardiography. After correct placement of the cannulas the skin was closed (Fig. 1).

Later this mode of cannulation was changed to central cannulation. A two-stage cannula was inserted in the right atrium and an arterial cannula in the ascending aorta after

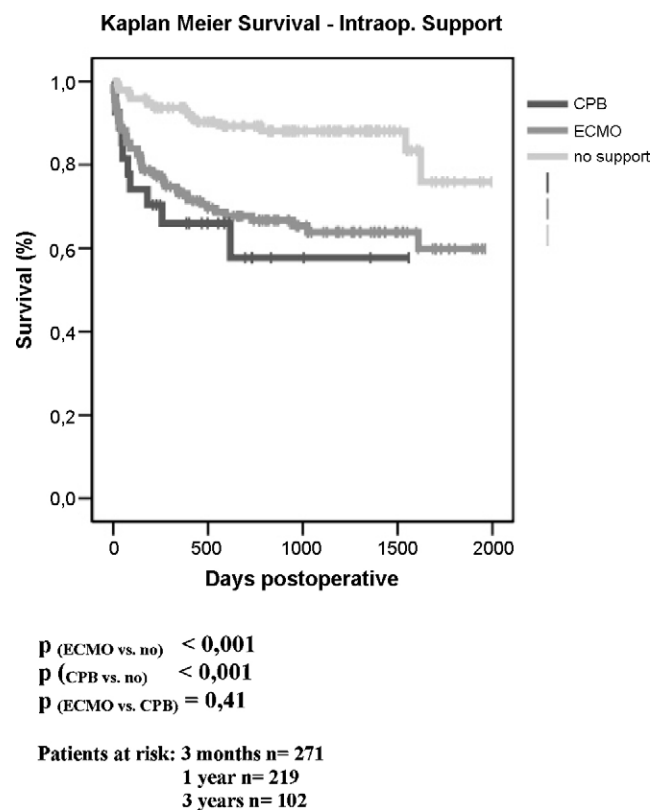


Fig. 1. Kaplan Meier Survival stratified by intraoperative support.

placement of appropriate cannulation sutures. After implantation of the lung(s), ECMO was gradually reduced and finally crossclamped. Patients were decannulated and the venous and arterial tubes of the ECMO were connected with each other and the ECMO system was left sterile at the table circulating by itself until the patient left the operating room. This provided the possibility to reinsert the same ECMO system in the groin for prolonged support in case of deteriorating graft function.

ECMO use was considered as prolonged if the patient had intraoperative ECMO support and left the OR with a running ECMO system. If ECMO has to be (re-)inserted on the ICU after the patients left the OR it was considered as postoperative ECMO.

Indication for prolonged use of ECMO was either donor related (in case of marginal donor organ quality), recipient related (in high risk patients, especially with elevated pulmonary artery pressure) or was set intraoperatively during the early reperfusion period (in case of progressively deteriorating graft function with decreasing oxygenation index and/or rising pulmonary artery pressure).

In case of postoperatively required ECMO the device was inserted on the ICU with no need to transport the patient to the operating room. A veno-arterial femoro-femoral approach was used as described above.

During ECMO support oxygen saturation was continuously monitored at the right upper limb and the cannulated lower limb. Mechanical ventilation with biphasic positive airway pressure was continued throughout the ECMO period. Due to the ECMO support protective low tidal volume and low maximum pressure ventilation was possible. ECMO flow was never reduced below 1 l/min until explantation to avoid the risk of intracannular clotting. Patients were evaluated at least on a daily basis for the possibility of weaning and removal of ECMO. After prolonged or postoperative support the ECMO system was routinely removed in the ICU and the vessels were reconstructed.

3. Results

3.1. Indications and demography

During the observation period a total of 306 patients were transplanted (199 DLTX, 58 SLTX, 49 Split lung/Lobar TX). Indications for lung transplantation were COPD ($n = 121$), pulmonary fibrosis ($n = 60$), cystic fibrosis ($n = 54$), pulmonary hypertension ($n = 41$), bronchiectasis ($n = 5$) and various other indications ($n = 25$). The use of ECMO was highly

Table 1
Indications for lung transplantation

	<i>n</i> (total)	ECMO support (%)	Intraoperative ± prolonged (%)	Postoperative only (%)
PH	41	78.0	73.2	4.8
Cystic fibrosis	54	62.9	59.3	3.6
Fibrosis	60	56.6	53.3	3.3
Bronchiectasis	5	40.0	40.0	0.0
COPD/emphysema	121	26.5	21.6	4.9
Other	25	57.1	52.4	4.7

Table 2
Patient demography – comparison ECMO vs no ECMO group

	ECMO	No ECMO	<i>p</i>
Age	42 ± 16	49 ± 13	<0.01
Gender (f/m)	66/81	66/93	n.s. (0.55)
Mean waiting list time (day)	87 ± 86	96 ± 84	n.s. (0.45)
Lobar/split lung TX (<i>n</i>)	39	10	<0.001

dependent on the indication for transplantation and is summarised in Table 1. Patient demography is shown in Table 2. Patients in the ECMO group had a significantly different spectrum of indications for lung transplantation and were significantly younger than in the non ECMO group due to the high rate of patients with pulmonary hypertension and CF. Furthermore the rate of technically more complex lobar and split lung procedures was significantly higher in the ECMO group.

3.2. Technique

ECMO was used in 147 patients in total (Table 3). Two patients were bridged to transplantation. A total of 130 patients including the two-bridged patients received intraoperative ECMO support. In 112 cases the necessity of ECMO was foreseen at the beginning of the operation and ECMO was prospectively installed. In 18 patients ECMO had to be installed during the operation due to haemodynamic or respiratory instability. In 51 of these patients ECMO was prolonged into the perioperative period. Five of these patients required ECMO support again in the postoperative period due to graft dysfunction. Cannulation site was central in 49 patients, central followed by femoro-femoral in 27 and femoro-femoral in 71 patients (Fig. 3).

CPB was used in 27 patients either due to concomitant cardiac defects or because a high blood turnover was anticipated based on previous operations with significant adhesion. Eleven of these patients needed therapeutic ECMO in the further course.

A total of 149 patients without relevant risk factors were transplanted without any intraoperative extracorporeal support. Six of these patients required ECMO support in the postoperative period for treatment of PGD.

3.3. Outcome

Median intubation times, ICU stay and hospital stay are outlined in Table 4. As one would expect the median

Table 3
Overview of ECMO and CPB use

	Bridge to TX	Intraoperative	Prolonged	Postoperative
	↓	↓	↓	↓
⇒ ECMO	2	130	51	5
⇒ CPB+ECMO		27	0	11
⇒ No support		149	0	6

Table 4
Comparison of hospital data

Data presented as median (range)	Intubation time (days)	ICU stay (days)	Hospital stay (days)
Preoperative ECMO (group I)	13.5 (12–15)	18 (16–20)	55.5 (41–70)
Intraoperative ECMO (group IIA)	4 (1–109)	11.5 (1–137)	25.5 (1–173)
Prolonged ECMO (group IIB)	7 (1–44)	12 (1–55)	26 (1–100)
CPB (group III)	17.5 (2–67)	23.5 (10–87)	51 (26–87)
No support (group IV)	1.5 (0–50)	5.5 (1–55)	23 (8–124)
Postoperative ECMO (group V)	8 (1–60)	15 (3–87)	26 (17–87)
<i>p</i> value			
ECMO vs CPB (II vs III)	0.32	0.06	0.02
ECMO vs no (II vs IV)	<0.01	<0.01	0.13
CPB vs no (III vs IV)	<0.01	<0.01	<0.01

intubation time and ICU stay of the patients transplanted on ECMO (IIA + B) was significantly longer compared to those patients with no support (group IV), however, overall hospital stay was comparable and only significantly longer in the CPB group (III).

Mean duration of postoperative ECMO was 46 ± 36 (range 8–168 h). Mean duration of ECMO was significantly ($p = 0.012$) longer in those patients receiving therapeutic ECMO for PGD (78 ± 47 h) compared to those with prophylactic prolonged use of ECMO (37 ± 29 h). In patients requiring therapeutic ECMO, implantation was performed 0–17 days post-transplant (mean 2 ± 5 days). Three of those patients required ECMO implantation later than 72 h after transplantation. Three patients underwent retransplantation while on postoperative ECMO support.

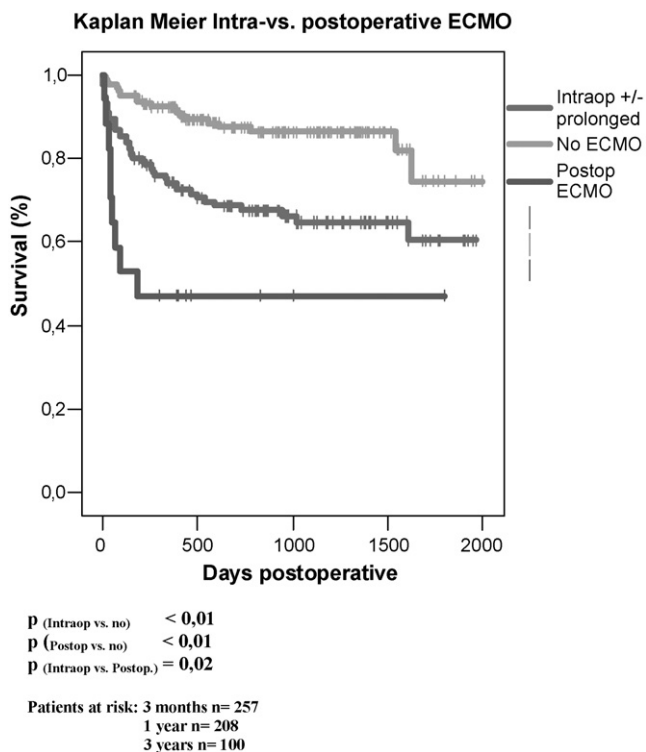


Fig. 2. Kaplan Meier Survival – intraoperative ± prolonged vs postoperative ECMO support.

3.4. Complications

Postoperative revision due to bleeding was required in 31 patients in the ECMO group compared to 7 patients in the CPB group and 11 patients in the group without support ($p = 0.001$). Vascular complications related to ECMO were observed in six patients. (Three patients required vascular grafts in the groin, one patient had to undergo a crossover bypass. One patient developed a retrograde aortic dissection requiring replacement of the ascending aorta and one patient needed a fasciotomy.) Four patients required revision of the groin due to thrombosis of a cannula or bleeding without further consequences. In two patients air was suctioned into a centrally inserted venous ECMO cannula causing the ECMO system to stop and requiring a switch to CPB. Two patients developed cerebral bleeding intraoperatively, which might potentially have been ECMO-related due to coagulation disturbances. However, based on the low heparinisation of the patients this is unlikely and the exact cause remains in question. Ten patients with peripheral insertion of ECMO cannulas developed a lymphatic fistula requiring surgical revision. This sums up to 25 complications (17%) in total. Complication occurred significantly more often with peripheral cannulation compared to central cannulation ($p = 0.012$).

3.5. Survival

Overall 3-month, 1-year and 3-year survival rates were 88.6%, 82.1% and 74.63%. The mentioned survival rates were

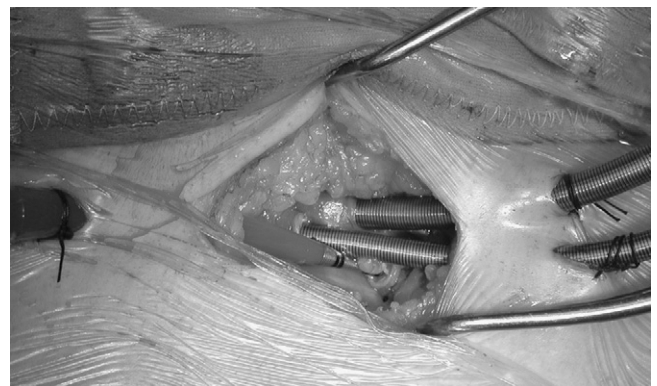


Fig. 3. Situs of veno-arterial femoro-femoral ECMO cannulation with separate leg perfusion cannula.

85.4%, 74.2% and 67.6% in the intraoperative \pm prolonged ECMO group (II); 93.5%, 91.9% and 86.5% in the no support group (IV) and 74.0%, 65.9% and 57.7% in the CPB group (III) (p (II vs III) = 0.41; p (II vs IV) < 0.001; p (III vs IV) < 0.001). In group V requiring postoperative ECMO survival rates were 52.9%, 47.0% and 47.0% (p all groups vs V < 0.05) (Figs. 1–3).

4. Discussion

The first report on the use of ECMO in lung transplantation dates back to 1978 [5]. Soon its application for graft failure after lung transplantation became an accepted indication [6,7] and also its use as a bridge to transplant was reported [8]. Both indications became routine applications for the use of ECMO. Especially for its use in early graft failure within 24 h after transplantation, impressive results have been reported [9].

However, if intraoperative extracorporeal support is required, cardiopulmonary bypass is the standard method which is advocated by various groups [10,11]. There is one report even describing a survival benefit for patients operated on CPB due to immunosuppressive effects [12]. One of the main reasons for the use of CPB is the avoidance of volume overflow of the first implanted lung potentially resulting in increased ischaemia-reperfusion oedema in bilateral lung transplantation.

On the other hand there is so far only limited experience with the intraoperative use of ECMO in lung transplantation. Only reports by two groups on small numbers of patients or selected patient collectives are described in the literature [1–3]. We reported our experience with the perioperative use of ECMO in PPH patients and found it extremely beneficial for initial organ function [3]. Since a significant amount of volume is bypassed by the lung optimal controlled reperfusion [13,14] can be achieved with the additional benefits of non-aggressive ventilation [15]. Additional potential benefits of ECMO over cardiopulmonary bypass are the avoidance of full heparinisation due to the heparin coated cannulas and the potential to prolong the support beyond the operation itself. Based on these results we implied routinely the use of veno-arterial ECMO in patients requiring extracorporeal support during the transplant procedure. Since then we acquired a large experience with the use of ECMO in lung transplantation and this is the first report on the routine use of ECMO instead of CPB in a large consecutive series of patients.

ECMO as a bridge to transplant was required only in two cases during the observation period. Both patients were suffering from CF and required ECMO due to progressive respiratory failure with failure to provide adequate gas exchange with conventional respirator therapy. ECMO was in both cases running intraoperatively and postoperatively prolonged. Both patients were successfully weaned from ECMO 1 day and 3 days after transplantation. One patient died 2 months postoperatively due to sepsis, the other patient is still alive.

Whether intraoperative support will be required is possible to estimate in most cases. One hundred and twelve patients were put on ECMO at the beginning of the operation.

Only in 18 cases (5.8%) we had to install ECMO due to respiratory or haemodynamic instability during the transplant procedure. Patients were always transplanted in normothermia. Initially we cannulated all patients via the femoro-femoral route. However, in some patients venous drainage was not as good as one could expect especially during manipulations to properly expose the hilum for the anastomoses. Another potential drawback was a considerable local morbidity in the groin with vascular complications and lymphatic fistulas. These considerations led to a change in the intraoperative application with central cannulation as the preferred implantation site, which avoids the potential complications in the groin if support is required only intraoperatively. It is possible to centrally cannulate the patient via the right thoracotomy, however in most cases a clamshell incision was performed if central cannulation was required. After implantation of the lung(s), ECMO is gradually reduced and finally cross-clamped. Patients are decannulated and the venous and arterial tubes of the ECMO are connected with each other and the ECMO system is left sterile at the table circulating by itself until the patient leaves the operating room. This provides the possibility to reinsert the same ECMO system in the groin for prolonged support in case of deteriorating graft function.

If poor initial graft function was to anticipate, we prophylactically prolonged ECMO support into the perioperative period. Factors influencing this decision were the quality of the donor organ with prolongation in most recipients of marginal donor lungs, high risk recipients especially with elevated pulmonary artery pressure as well as an intraoperative situation with low or continuously decreasing oxygenation index especially if combined with a high or rising pulmonary artery pressure.

As any invasive therapy, ECMO support has the potential for complications. Initially we observed a relatively high incidence of postoperative intrathoracic bleeding complications in patients on postoperatively prolonged ECMO. The main reason for this phenomenon was the reduction in thrombocyte count deriving from the combination of ATG induction therapy and prolonged ECMO. Avoidance of this combination or, if absolutely required, aggressive substitution of thrombocytes resulted in a significant reduction of bleeding complications.

Comparability of patients requiring ECMO support to those transplanted without any extracorporeal support is limited, since the group of patients transplanted on ECMO represent the clearly more difficult collective, including many PH patients who are known to have inferior survival rates compared to other indications. Patients in the ECMO group therefore represent a selection of the most complex cases, which do not surprisingly need longer periods to recover and have less favourable outcome. This is also confirmed by our in-hospital data, which demonstrate that the median intubation time and ICU stay of patients transplanted on ECMO is significantly longer compared to patients transplanted without ECMO, however the overall hospital stay is comparable in both groups.

As one would expect, in patients needing ECMO for primary graft dysfunction, outcome is significantly worse compared to all other groups. Our results are still in the upper

range compared to other publications dealing with this topic, however survival rates still remain limited. Main cause of early mortality in those patients ultimately is multi-organ-failure. Conduct of ECMO in this indication is controversially discussed in the literature. One report suggests a lower complication rate with veno-venous approach [16], whereas other groups change their technique from case to case [17]. We prefer the veno-arterial approach in this indication, which also provides relief of the pulmonary circulation, since the impaired graft function almost uniformly is accompanied by a rise in pulmonary arterial pressure. Regardless of the ECMO implantation site the reported outcomes are uniformly bad if ECMO is initiated later than 7 days post-transplant [18], because in most of these cases the occurring problem is not related to PGD but rather to other complicating factors such as rejection or infection.

5. Conclusion

ECMO is a valuable tool in lung transplantation providing the potential to bridge patients to transplantation, to replace CPB with at least equal results and to overcome severe postoperative complications. Favourable survival rates can be achieved despite the fact that ECMO is used in the more complex patient population undergoing lung transplantation as well as to overcome already established severe complications.

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Appendix A. Conference discussion

Dr L.K. von Segesser (Lausanne, Switzerland): When you switch from perioperative ECMO to postoperative or prolonged ECMO, cannulation is probably not exactly the same, not only in sites but also in direction, because you have to think about the extremities. Can you elaborate on that?

Dr Aigner: Well, as I pointed out, in the early period we routinely cannulated in the femoral vessels, and if postoperative support was required, we simply left the ECMO system running on the same side. Later on we altered our regimen and we routinely cannulated intraoperatively if we anticipated that the support will be required for the intraoperative period only. However, if postoperative support was required, we always cannulated in the groin. We expose the femoral vessels and inserted the cannulas in the common femoral artery and in the femoral vein.

Dr von Segesser: But what about distal perfusion?

Dr Aigner: In the case of a small arterial diameter and if the arterial perfusion would be compromised, we inserted a leg cannula. However, this was only done if due to a small artery insertion of a leg perfusion cannula was required. If the artery was large enough, we did not insert a leg perfusion cannula.

Dr C. Yankah (Berlin, Germany): First, how long was the waiting time for those patients who were bridged to lung transplant? My second question is the ischaemic time of the lung donor and the timing and criteria for implantation of the ECMO after the lung transplantation in the postoperative phase?

Dr Aigner: Those two patients we bridged to transplant with ECMO both were high urgent patients within Euro transplant and waited for less than one week for their transplantation. And we did not analyse the ischaemic times of all the patients.

Dr D. Van Raemdonck (Leuven, Belgium): First, what is your indication to install ECMO postoperatively in the first, let's say, 24 h after lung transplantation in case of primary graft dysfunction? And second, I understand you switched from femoral to central cannulation. How easy is this to cannulate in a patient when you are doing a bilateral lung transplantation through an anterior thoracotomy?

Dr Aigner: Well, first of all, our exact indication to install postoperative ECMO, I can't give you an exact value which is true for all patients. We tend to implant ECMO very early if we see a beginning graft failure. If the ventilatory support is rising, if we see the pulmonary artery pressures rising and we might anticipate that the patient may go into severe primary graft dysfunction, we relatively aggressively implant ECMO within the first 24 h. Actually except for

three patients who were put on ECMO later on in the postoperative period, all of our postoperative patients were put on ECMO within the first 24 h after transplantation.

Dr A. Sosnowski (*Leicester, United Kingdom*): I understand all ECMO support was veno-arterial ECMO. Is that right?

Dr Aigner: Yes, this is correct.

Dr Sosnowski: Why don't you use venovenous ECMO?

Dr Aigner: We have the experience that especially in the early postoperative phase it is beneficial to also provide the right cardiac support with veno-arterial ECMO. We had good experiences with veno-arterial ECMO and we didn't see any need currently to switch to a venovenous implantation only.