Bilateral lung transplantation with intra- and postoperatively prolonged ECMO support in patients with pulmonary hypertension

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Abstract

Objective: Lung transplantation for pulmonary hypertension (PH) is usually performed on cardiopulmonary bypass, with the disadvantage of full systemic anticoagulation, uncontrolled allograft reperfusion and aggressive ventilation. These factors can be avoided with intra- and postoperatively prolonged extracorporeal membrane oxygenator (ECMO) support. Patients and methods: Between February 1999 and March 2001, 17 consecutive patients with PH (systolic pulmonary artery pressure > 70 mmHg) of different etiologies underwent bilateral lung transplantation (BLTX). There were 11 females and six males in the age range from 7 to 50 years (mean age, 28.4 ± 12.9 years). Six patients were preoperatively hospitalized, four in the intensive care unit (ICU), one was on ECMO for 3 weeks pretransplantation, and one was resuscitated and bridged with ECMO for 1 week until transplantation. Femoral venoarterial ECMO support with heparin-coated circuits was set up after induction of anesthesia and discontinued at the end of surgery (n = 3) or extended for 12 h median into the postoperative period (n = 14). Postoperative ventilation pressure was kept below 25 mmHg. Allograft function at 2 h after discontinuation of ECMO, outcome and adverse events were monitored in all patients. Mean follow up time was 18 ± 11.4 months. Results: The perioperative mortality was 5.9% (n = 1). Arterial oxygen pressure measured 2 h after weaning from ECMO, and under standard mechanical ventilation with a peak pressure of 25 mmHg and inspired oxygen fraction of 0.4, was 157 ± 28 mmHg. The mean pulmonary artery pressures were reduced to 29 ± 3.4 from 66 ± 15 mmHg before transplantation. Postoperative complications included rethoracotomy due to bleeding (n = 4) and temporary left ventricular failure (n = 4). Median ICU stay was 12 days. Incidence of rejection within the first 100 days was 0.4 per patient. Conclusion: BLTX with intraoperative and postoperatively prolonged ECMO support provides excellent initial organ function due to optimal controlled reperfusion and non-aggressive ventilation. This results in improved outcome even in advanced forms of PH. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Lung transplantation; Pulmonary hypertension; Cardiopulmonary bypass; Extracorporeal membrane oxygenation

1. Introduction

Bilateral sequential lung transplantation (BLTX) is a routine surgical procedure and an established therapeutic option in endstage lung disease. In patients with elevated pulmonary artery pressure, it is usually performed on cardiopulmonary bypass (CPB), which allows for intraoperative haemodynamic stability and avoids the initial over-flow of the first implanted lung [1–3]. However, it has been demonstrated that CPB itself can lead to impairment of lung function in patients undergoing open heart surgery [4,5]. The main disadvantages of CPB are the need for full systemic anticoagulation and the high blood turnover in the suction system, which results in recirculation of activated inflammatory mediators. In lung transplantation (LTX) – once CPB is discontinued – the
transplanted lungs are exposed to the complete cardiac output (CO). Particularly in patients with pulmonary hypertension (PH), this can have a profound negative impact on early allograft function, and in some cases results in a need for aggressive ventilation with high tidal volumes and pressures.

All these factors can be avoided by the use of intra- and postoperatively prolonged extracorporeal membrane oxygenation (ECMO) support.

The objective of this retrospective study was to investigate efficacy and safety of the use of intra- and early postoperative prolonged ECMO on pulmonary allograft function in patients with different forms of PH undergoing BLTX.

2. Patients and methods

2.1. Patients demographic

Between February 1999 and March 2001, 17 consecutive patients with PH (systolic pulmonary artery pressure (PAPsys) > 70 mmHg) of different etiologies underwent various forms of BLTX, including split lung as well as cadaveric lobe transplantation (Table 1). Within the study period, all patients with the diagnosis of PH received ECMO support at the time of transplantation. Additional surgical procedures at the time of transplant were performed in three patients (pulmonary aneurysm repair, n = 1; closure of patent foramen ovale, n = 2). The cause of lung disease was primary pulmonary hypertension (PPH, n = 10), cystic fibrosis (CF, n = 4), chronic obstructive pulmonary disease (COPD, n = 1), fibrosis due to graft versus host (GVH) disease n = 1, secondary pulmonary hypertension (SPH) after pulmonary trombendarterectomy (PTEA) (n = 1). The systemic and mean pulmonary artery pressure of the study population were 100.8 ± 26.1 and 66.1 ± 15.4, respectively. There was no statistically significant difference between patients with vascular and parenchymal lung disease with regard to pulmonary artery pressures.

Six patients were preoperatively hospitalized: four in the intensive care unit (ICU), one was on ECMO for 3 weeks pretransplantation, and one was resuscitated and bridged with ECMO for 1 week until transplantation (TX).

Eleven patients suffered from comorbid conditions like impaired renal (creatinine clearance <0.4 mL/s) and hepatic function (elevated hepatic laboratory tests associated with or without ascites), diabetes and malnutrition (less then 60% of predicted body mass index, BMI).

2.2. BLTX technique

All donor lungs were harvested en bloc as part of a multiorgan procurement and preserved inflated in a low potassium dextran extracellular solution. BLTX was performed by a standard technique through bilateral anterior thoracotomies [6]. Donor lungs were implanted using 4-0 polydioxanone suture (PDS) single running sutures for the bronchial anastomosis and 5-0 Prolene for the pulmonary artery and the left atrial anastomoses. After completion of the vascular anastomoses, the graft was flushed retro- and then antegrade. Ventilation of the transplanted lungs was started at the time of reperfusion.

2.3. ECMO management

All patients were placed on ECMO using the same protocol and technique. ECMO support was set up through the femoral venoarterial route after induction of anesthesia. After exploration of the femoral artery and vein, the size of the cannulas was carefully selected, in order not to compromise the distal femoral arterial flow. In case of small arterial diameter and complete occlusion of the vessel

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Gender</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Technique</th>
<th>PAP mean/systolic</th>
<th>Follow up (months)</th>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>27</td>
<td>PPH</td>
<td>BLTX</td>
<td>60/80</td>
<td>29</td>
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<td>2</td>
<td>F</td>
<td>24</td>
<td>PPH</td>
<td>Split LT</td>
<td>102/68</td>
<td>Died on POD 7</td>
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<td>3</td>
<td>F</td>
<td>49</td>
<td>SPH after PTEA</td>
<td>BLTX</td>
<td>100/42</td>
<td>21</td>
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<td>F</td>
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<td>PPH</td>
<td>BLTX</td>
<td>147/84</td>
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<td>5</td>
<td>F</td>
<td>34</td>
<td>PPH ± PA</td>
<td>BLTX ± PA repair</td>
<td>105/65</td>
<td>19</td>
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<td>6</td>
<td>M</td>
<td>22</td>
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<td>BLTX with cadaveric lobes</td>
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<td>8</td>
<td>M</td>
<td>50</td>
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<td>BLTX</td>
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<td>M</td>
<td>21</td>
<td>PPH ± foramen ovale</td>
<td>BLTX ± repair of foramen ovale</td>
<td>90/70</td>
<td>13</td>
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<tr>
<td>10</td>
<td>M</td>
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<td>PPH</td>
<td>BLTX</td>
<td>145/83</td>
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<td>F</td>
<td>14</td>
<td>CF</td>
<td>BLTX</td>
<td>135/83</td>
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<td>12</td>
<td>F</td>
<td>13</td>
<td>CF</td>
<td>BLTX</td>
<td>120/82</td>
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<td>13</td>
<td>F</td>
<td>7</td>
<td>F due to GVH</td>
<td>BLTX with cadaveric lobes</td>
<td>105/72</td>
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<td>Died on POD 140</td>
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<tr>
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<td>COPD</td>
<td>BLTX</td>
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<td>21</td>
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<td>BLTX</td>
<td>70/43</td>
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<td>F</td>
<td>45</td>
<td>CF</td>
<td>BLTX</td>
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by the arterial cannula, a separate cannulation of the distal limb was performed (Fig. 1).

The whole ECMO apparatus was obtained from Medtronic Inc., and consisted of the Medtronic Carmeda heparin-bound system, a Medtronic Maxima hollow-fiber oxygenator, a Bio-Medicus BP-80 centrifugal pump, a flow probe and 3/8-inch internal diameter heparin-bound tubing. Because of the heparin-bound tubing sets, systemic administration of heparin was not used except for an intravenous bolus of 50 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. Oxygen saturation of the right upper limb and the cannulated lower limb was continuously monitored.

After induction of general anesthesia, a complete haemodynamical investigation was performed. ECMO flow was set at 50% of the predicted CO. After implantation of the first lung graft, ECMO flow was adjusted to keep the mean pulmonary artery pressure below 35 mmHg, end-tidal carbon dioxide pressure around 20 mmHg to achieve an arterial oxygen pressure (PaO$_2$) of at least 75 mmHg in the right radial artery.

In three patients, ECMO was discontinued immediately after the conclusion of the operation, and in the remaining 14 patients, ECMO support was prolonged for a minimum of 6 h postoperatively.

Thereafter the flow was decreased to 50% followed by a reduction to 25 and 0% in two intervals of 3 h each. Then the ECMO cannulas were removed in the ICU and the femoral vessels primarily repaired.

Blood gases were monitored 2 h after the removal of the ECMO, with the patients on standard mechanical ventilation with a positive end expiratory pressure of 8 cm H$_2$O, peak pressure <25 cm H$_2$O, rate of 12, inspirium–expirium ratio (I/E) ratio of 0.5, and inspired oxygen fraction (FiO$_2$) of 0.4. Thereafter patients were weaned off mechanical ventilation depending on the clinical situation.

2.4. Immunosuppression

All patients were treated with standard immunosuppression protocols based upon calcineurin inhibition with tacrolimus/cyclosporine, mycophenolat mofetil and prednisone. Methylprednisolone at a dose of 1000 mg i.v. was given intraoperatively and followed by 125 mg every 8 h for three doses postoperatively. Calcineurin inhibition was instituted immediately postoperatively and the dose adjusted to achieve a trough level of 15–18 ng/ml for tacrolimus and 350–450 ng/ml for cyclosporine, respectively.

Induction therapy consisted of rabbit antithymocyte globulin (ATG) at a dose of 2.5 mg/kg maintained for 6 days (adjusted for white blood cell and platelet count) in six patients, and daclizumab in three patients. The daclizumab group received an infusion of daclizumab of 1 mg/kg intraoperatively before reperfusion of the graft, and again on days 14, 28, 42, and 56 in three patients. The remaining eight patients received no induction immunosuppression.

3. Results

3.1. Perioperative mortality

The perioperative mortality was 5.9% (n = 1). Only one patient died on the 7th postoperative day due to acute left ventricular failure (LVF) at the time of extubation. His underlying disease was severe PPH.

3.2. Late mortality

One patient with advanced PPH died late after transplant (5.9%). The patient was resuscitated while on the TX waiting list and bridged on ECMO thereafter for 7 days until a suitable organ for TX was available. Although the TX was uneventful, severe hypoxic cerebral damage was detected in computed tomography (CT) and magnetic resonance imaging (MRI) scans at the time of weaning and the patient eventually died 5 months posttransplantation without regaining consciousness.

All other patients are alive and well with a mean follow up of 18 ± 11.4 months.

3.3. Perioperative morbidity

Four patients underwent reoperation for hemothorax. In four patients with severe PPH1 [including the one who died on postoperative day (POD) 7], temporary LVF was observed at the time of weaning. With a combination therapy of betamimetics, fluid restriction and elevation of the upper body, it was possible to overcome the problem in all but one patient.

Exposure of the femoral vessels led to lymph fistulas in two instances. Both were treated by radiation therapy and...
healed within 2 weeks. There were no vascular problems in the repaired vessels.

3.4. Early functional results

Duration of ECMO support, intubation, and stay in the ICU are depicted in Fig. 2. All patients had an excellent oxygenation 2 h after ECMO discontinuation, with a mean partial PaO₂ of 157 ± 28 mmHg on standard mechanical ventilation with FiO₂ of 0.4 and peak pressure of 25 mmHg and a rate of 12 ventilatory cycles per min. The mean pulmonary artery pressures were reduced to 29 ± 3.4 from 66 ± 15 mmHg before transplantation. The mean CO of 3.7 ± 0.51 L/min pretransplant was increased to 6 ± 0.52 L/min after surgery (Fig. 3).

3.5. Late functional outcome

The incidence of rejection during the first 100 days was 0.4 per patient. The overall incidence of infection during the same period was 2.1 per patient (bacterial infections 0.9, viral 0.7 and fungal 0.5, respectively).

One patient developed bronchiolitis obliterans syndrome (BOS) I during the investigation period. Another patient had an episode of invasive aspergillus infection 1.5 years after LTX, which was successfully treated by i.v. amphotericin B. However, this infection resulted in severe impairment of lung function, and the patient underwent successful retransplantation, eventually.

4. Discussion

Patients with significantly elevated pulmonary artery pressure (PAP) undergoing BLTX have a higher incidence of perioperative complications [2,7].

When the operation is performed without CPB, the first transplanted lung is subjected to the complete CO during the implantation of the second lung. Even if CPB is used during the implantation procedure, the chronically trained right heart with its muscular hypertrophy will deliver the blood flow with increased mechanical shear stress to the lungs immediately after discontinuation of CPB. This can lead to the well-known phenomenon of reperfusion edema in various degrees. CPB itself has the disadvantage of a high blood turnover in the suction system and recirculation of activated inflammatory mediators [4,8]. Five out of eight patients of a historical control, who underwent BTLX for PPH at our department prior to the study period developed severe pulmonary edema after surgery. Two patients died perioperatively.

Once a lung allograft has developed reperfusion edema, the further treatment strategy focuses on ventilation with high pressures to minimize the production of intraalveolar fluid. However, this ventilation technique itself is associated with negative effects on the lung. Traditional approaches to mechanical ventilation use tidal volumes of 10–15 ml per kg of body weight. These volumes are larger than those in normal subjects at rest (range 7–8 mL/kg), but they are frequently necessary to achieve normal values of oxygenation. However, in animal experiments, it has been demonstrated that ventilation with the use of such large tidal volumes causes disruption of pulmonary epithelium and endothelium and subsequently leads to lung inflammation and release of inflammatory mediators [8,9]. A similar experience has been gained in clinical settings. In a controlled, multicentre randomized trial of the acute respiratory distress syndrome (ARDS) network on 861 patients with acute lung injury or ARDS, the authors demonstrated that a less aggressive respiratory pattern with lower tidal volumes as traditionally used resulted in improved clinical outcome [10]. These data support the view that aggressive ventilation patterns – although sometimes necessary to provide adequate oxygenation – contribute to exacerbation and perpetuation of lung injury [4,10]. On the contrary, by use of lower tidal volumes, mechanical lung damage can be avoided.

During the last decade, experience has been gained with the use of ECMO for treatment of severe reperfusion injury after LTX [11–13]. Meyers et al. reviewed 12 patients and reported that ECMO can provide effective therapy for acute posttransplantation lung dysfunction [14]. Similar results have been reported by Zenati et al. who reviewed the experi-
ence of the University of Pittsburgh with ECMO for primary severe allograft dysfunction in eight patients after LX [15]. They observed 87% success rate for weaning from ECMO with a low incidence of complications. In all these cases, ECMO was used to treat already established posttransplant lung dysfunction.

There is only one single report in the literature, where prolonged ECMO was used prophylactically, in an attempt to avoid lung injury in the early postoperative period.

Ko et al. [16] reported their experience in five patients with PPH, where they used ECMO during LTX and for few hours thereafter. All patients had an uneventful TX and showed an excellent organ function after the procedure.

Additional data on the importance of controlled reperfusion have derived from experimental studies. In an early experimental work by Allen et al. [17], it was demonstrated that 20 min of controlled reperfusion is superior to 10 min of reperfusion. Bhabra et al. proved that reduction of pulmonary artery pressure during the first 10 min of reperfusion leads to a clear reduction in an incidence of pulmonary reperfusion injury [18].

These experimental findings are now implemented in clinical routine of the LTX, where the pulmonary artery is only partially released during the first 10 min of reperfusion [19,20].

In view of this concept, venoarterial ECMO offers the advantage to bypass a significant part of CO to the pulmonary vascular bed. This results in a reduction of perfusion pressure and less mechanical shear stress and endothelial damage.

Besides its haemodynamical effect in the early reperfusion period, ECMO support, prolonged for several hours, allows to ventilate the lungs extremely carefully. By keeping positive end-expiratory pressure (PEEP) and peak pressure limited, the negative effects of aggressive ventilation described above can be avoided. In addition to these mechanical effects, fully heparinized ECMO systems avoid the need for complete heparinization, for suction and for return of aspirated blood.

The patients in this study comprise a consecutive series of all patients with PAPsys > 50 mmHg undergoing BLTX within the investigated period. By indication, a fairly high number of high-risk patients who underwent advanced technical TX procedures are included. In view of this background, the perioperative mortality was favourably low. More importantly, the functional performance of the transplanted lungs as expressed by PaO2 levels under defined ventilation conditions, 2 h after ECMO discontinuation, was excellent. In our opinion, both factors are the result of the beneficial effect of ECMO.

With regard to the complications, the four observed cases of rethoracotomy for intrathoracal bleeding, have to be discussed.

A lower thrombocyte count is a potential side effect of ECMO. Especially in combination with ATG, this can be become clinically relevant. In fact, all four patients who underwent rethoracotomy, had diffuse bleeding as bleeding source and thrombocyte counts were below 100 000/\mu L. As a consequence, we suggest to either substitute thrombocytes or to avoid induction therapy with ATG in this clinical setting.

There has been evidence in literature [21–23] that initial endothelial damage and the enhanced presentation of donor antigens to the immunesystem, can result in higher frequencies of acute rejections and late graft deterioration.

In fact, the incidence of rejection observed in our patients is on the lower range reported in literature [21,24,25,26]. Whether this effect can also have an impact on a lower incidence of BOS in the long term cannot be answered from these data yet. In conclusion, in this retrospective study in patients with different forms of PH, undergoing BLTX with intra- and postoperative ECMO support, excellent early allograft function was demonstrated. This supports the concept that optimal reperfusion conditions can be achieved by the use of ECMO due to the combination of controlled reperfusion and the use of less aggressive ventilation patterns.

From this data, we would advocate the use of ECMO as a support system during BLTX in patients with different forms of severe PH.

References

[10] The Acute Respiratory Distress Syndrome Network. Ventilation with...


