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# Extracorporeal membrane oxygenation for lung transplant recipients with primary severe donor lung dysfunction

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**Abstract** Primary severe donor lung dysfunction (DLD) is a significant complication after lung transplantation (LTx), and a high mortality is reported with conventional therapy. The purpose of this report is to review the experience of the University of Pittsburgh with extracorporeal membrane oxygenation (ECMO) for primary severe DLD after LTx. From September 1991 to May 1995, 220 LTx were performed at our center. Eight patients (8/220 = 3.6 %) with severe DLD after LTx required ECMO support. The age of LTx recipients was 44 ± 5 years (mean ± SD); seven patients were female and one was male. Indications for LTx were: chronic obstructive pulmonary disease in four patients, bronchiectasis in two, and pulmonary hypertension in two. There were three single LTx and five bilateral LTx. The interval from LTx to institution of ECMO was 5.6 ± 3.2 h (range 0–10 h). Three patients were supported with veno-venous (v-v) ECMO and five had veno-arterial (v-a) ECMO. The duration of ECMO support was 7.3 ± 4.8 days (range 3–15 days). activated glotting time (ACT) was maintained between 110 and 180 s with intermittent use of heparin. Seven patients (7/8 = 87 %) were successfully weaned from ECMO and six patients (6/8 = 75 %) were discharged home; they are currently alive after a follow-up of 17 ± 10.1 months. One patient died on ECMO support for refractory DLD and another died 2 months after ECMO wean from multisystem organ failure. At 6 months follow-up, forced expiratory volume in 1 s (FEV1) is 2.35 ± 0.9 l (75 % ± 17.4 % predicted) and mean forced vital capacity (FVC) is 2.53 ± 0.8 l (64 % ± 14 % predicted). We conclude that ECMO can be lifesaving when instituted early after primary severe DLD. The v-v ECMO support is preferred when the patient is hemodynamically stable and adequate long-term function of the allograft is anticipated.

**Key words** Lung transplantation, ECMO · Donor lung dysfunction

## Introduction

Lung transplant (LTx) recipients are at risk of donor lung dysfunction (DLD) at several stages after allograft implantation [6].

Primary severe DLD is defined as the immediate inability of a successfully revascularized pulmonary allograft to sustain ventilation and oxygenation despite maximal mechanical support; its prevalence in the LTx population ranges from 2 % to 12 % [7, 16]. Possible causes are listed in Table 1. In the great majority of cases, we are unable to identify a single cause that can explain the allograft failure, and we can only refer to these potential etiologies as risk factors. Success with

this group of patients has been reported by using extracorporeal membrane oxygenation (ECMO) [11, 13, 14].

Secondary DLD can be due to technical complications at the anastomosis, infection, or acute or chronic rejection and is not included in this analysis; our results with ECMO support in this subset of patients are dismal with none (0/7) alive [3].

We retrospectively analyzed our experience at the University of Pittsburgh with ECMO support for primary severe DLD in LTx recipients with the current preservation and support techniques.

## Materials and methods

### Patient population

The records of eight patients placed on ECMO for primary severe DLD within 12 h of LTx at the University of Pittsburgh from September 1991 to May 1995 were reviewed. During this period, 220 LTx were performed at our institution, giving a prevalence of primary severe DLD of 3.6 % (8/220).

The characteristics of these patients are summarized in Table 2. There were seven females and one male; their age was 44 ± 5 years (mean ± SD). Three patients had a single LTx and five had a bilateral single LTx. Three patients required support with cardiopulmonary bypass during the transplant procedure, two because of pulmonary hypertension and one for severe adhesions with bronchiectasis. Furthermore, one patient also required a brief period of circulatory arrest to repair a tear in a patent ductus arteriosus.

Surgical techniques for single and bilateral LTx have been described elsewhere [4]. Donor lungs were selected using strict criteria [15] (Table 3).

Graft preservation was accomplished with hypothermic flush of the pulmonary artery with 100 ml/kg of modified University of Wisconsin (UW) solution preceded by a bolus of 500 μg micrograms Prostaglandin-E1 (PGE1) [5]. Donor lungs were stored in University of Wisconsin solution and maintained inflated with O2 until implantation.

Ischemic time for the first graft (in the case of bilateral single lung) or for single lung was 266 ± 54.8 min; ischemic time for the second graft was 432 ± 101 min. These ischemic times were not significantly different from those of the general lung transplant population.

### Technique of ECMO

Criteria for institution of ECMO (Table 4) included: (1) severe hypoxemia on maximal mechanical ventilatory support and forced inspiratory oxygen (FIO2) of 1.0 (mean alveolar-arterial O2 gradient in our eight patients was 650 torr), (2) decreased static lung compliance (mean value 14 ml/cm H20), (3) persistent diffuse infiltrate on chest roentgenogram, and (4) evidence of diffuse alveolar damage on open lung biopsy, when available.

We routinely use a Carmeda BioActive Surface (CBAS)-coated system [1, 8–10] (Medtronic Cardiopulmonary, Anaheim, Calif.; Table 5). Oxygenation is provided by two parallel Carmeda Medtronic Maxima II hollow-fiber oxygenators. A Biomedicus pump and heparin-coated tubing are utilized. Oxygenators are changed when foaming occurs. activated glotting time (ACT) is kept between 110 and 180 s while on full-flow ECMO support. If the ECMO flow is reduced, the level of antithrombin III is monitored and fresh frozen plasma transfused as indicated [2]. Initial priming of the ECMO system is with plasmalyte A, which is then displaced with three units of cell saver washed bank blood, 75 mEq sodium bicarbonate and 500 mg of calcium chloride. Total priming volume is 1800–2200 ml. Cannulation is performed via a percutaneous method using Carmeda-coated cannulae or via the open "central" method. If the patient is hemodynamically stable, veno-venous (v-v) ECMO is preferred. The veno-arterial (v-a) ECMO is reserved for the more profoundly compromised patients.

During ECMO, the ventilator settings are maintained at a tidal volume of approximately 600 ml, a respiratory rate of 4 breaths/min, positive end-expiratory pressure of 10 cm H20, and FIO2 of 0.5; these are adjusted according to the arterial blood gas.

The mean interval from the completion of LTx to the initiation of ECMO was 5.6 ± 3.2 h (range 0–10 h).

In four patients, ECMO was started in the operating room and was performed through "central" cannulation (right atrium to ascending aorta); in these patients the interval was 4 ± 3.2 h. One patient was switched to v-v ECMO while the remaining three were weaned directly from "central" cannulation.

**Table 1** Risk factors for primary donor lung dysfunction

- Reperfusion injury
- Coagulopathy, multiple transfusions
- Prolonged ischemia
- Cardiopulmonary bypass
- Unrecognized underlying donor lung pathology
- Hyperacute rejection
- Multifactorial

**Table 2** Patient characteristics (*PDA* patient ductus arteriousus, *PPH*, primary pulmonary hypertension, *COPD* chronic obstructive pulmonary disease)

| Pathology | Sex | Age (years) | Transplant type |
|---|---|---|---|
| Eisenmenger's complex[a] | F | 45 | Bilateral single lung + closure PDA |
| Bronchiectasis | M | 39 | Bilateral single lung |
| Bronchiectasis[a] | F | 39 | Bilateral single lung |
| PPH[a] | F | 38 | Bilateral single lung |
| COPD | F | 47 | Left single lung |
| COPD | F | 50 | Right single lung |
| COPD | F | 50 | Left single lung |
| COPD | F | 48 | Bilateral single lung |

[a] Required cardiopulmonary bypass during transplant

**Table 3** Criteria for donor lung selection ($PaO_2$ arterial oxygen tension, $FIO_2$ forced inspiratory oxygen, *PEEP* positive end-expiratory pressure, *GM* gram)

- Clear chest roentgenogram
- $PaO_2 > 350$ torr on $FIO_2$ 1.0 and PEEP 5 cm $H_2O$
- Normal bronchoscopy
- Absence of aspiration
- No heavy fungus on sputum GM stain

**Table 4** Criteria for ECMO ($FIO_2$ forced inspiratory oxygen)

- Severe hypoxemia despite maximal ventilatory support on $FIO_2$ 1.0
- Widened alveolar-arterial $O_2$ gradient
- Decreased static lung compliance
- Persistent diffuse infiltrate on chest roentgenogram
- Evidence of diffuse alveolar damage on lung biopsy (when available)

**Table 5** Carmeda Bioactive Surface (CBAS)-ECMO System

- Carmeda-Medtronic Maxima II oxygenators
- Carmeda-Biomedicus BP-80 centrifugal pump
- 3/8″ ID × 3/32″ wall thickness Carmeda tubing
- Carmeda-coated cannulae

**Table 6** ECMO Experience (*v-a* venous-arterial ECMO, *v-v* veno-venous ECMO)

| Patient no. | Type of ECMO | Interval (hours)[a] | Duration (days)[b] | Weaned | Alive |
|---|---|---|---|---|---|
| 1 | Central v-a | 4 | 4 | Yes | Yes |
| 2 | Central v-a | 3 | 3 | Yes | Yes |
| 3 | Central v-a | 7 | 4 | Yes | Yes |
| 4 | Central v-a[c] | 6 | 11 | Yes | Yes |
| 5 | Percutaneous v-a[c] | 9 | 4 | Yes | Yes |
| 6 | Percutaneous v-v | 6 | 15 | Yes | No |
| 7 | Percutaneous v-a | 4 | 5 | Yes | Yes |
| 8 | Percutaneous v-a[c] | 10 | 13 | No | No |

[a] Time from LTx to start of ECMO
[b] Length of ECMO support
[c] Switched to percutaneous v-v

Four patients received ECMO support through percutaneous cannulation: one patient had v-v ECMO through the right internal jugular vein to the right femoral vein, while the other three had v-a cannulation of the right femoral vein to the right femoral artery because of hemodynamic instability. In these four patients with the percutaneous technique, the interval from LTx to initiation of ECMO was 7.2 ± 2.7 h.

The duration of ECMO support was 7.3 ± 4.8 days (range 3–15 days). The duration of support in patients with "central" ECMO was 5.5 ± 3.7 days, while the duration of support in percutaneous ECMO was 9.25 ± 5.5 days.

## Results

### Survival

Seven patients (7/8 = 87 %) were successfully weaned from ECMO (Table 6). One patient died after being on ECMO for 13 days for refractory severe DLD. This patient received a left LTx for chronic obstructive pulmonary disease and was started on percutaneous ECMO in the intensive care unit 10 h after LTx. Because there was no improvement, she underwent an open-lung biopsy to rule out accelerated allograft rejection, but the result demonstrated only severe diffuse alveolar damage. The patient was relisted for LTx while on ECMO. Due to lower limb ischemia she was switched to percutaneous v-v ECMO (right internal jugular vein to right femoral vein). She also developed acute renal failure requiring hemodialysis. After 13 days the patient developed marked refractory acidosis and ECMO support was discontinued. No autopsy was available.

Six patients (6/8 = 75 %) are currently alive after a follow-up of 17 ± 10.1 months. One patient died 3 months after having been weaned from ECMO from multisystem organ failure secondary to sepsis.

At 6 months follow-up, the forced expiratory volume in 1 s (FEV1) of the six survivors is 2.35 ± 0.9 l (75 % ± 17.4 % predicted) and the forced vital capacity (FVC) is 2.53 ± 0.84 l (64 % ± 14.5 % predicted). Four patients are on tacrolimus-based immunosuppression and two are on cyclosporin-based immunosuppression.

### Complications

Two patients with percutaneous v-a ECMO required a switch to percutaneous v-v ECMO for lower limb ischemia. The femoral artery was successfully repaired in both cases.

Four patients had significant bleeding during ECMO that required re-exploration and transfusion of blood products. Overall, the number of units of packed red blood cells transfused during ECMO was 15.6 ± 9.4.

One patient with bilateral single LTx for Eisenmenger's complex suffered from ischemic injury of the right bronchus requiring temporary stenting. This patient had "central" v-a ECMO for 4 days. In this patient we were able to calculate O2 consumpatiention (VO2) and CO2 excretion (VCO2) by respiratory gas analysis with a metabolic chart [12]. This lung VO2 represents the amount of O2 consumed by the lung tissues directly from the alveoli. This patient with bilateral LTx on full-flow ECMO provided, in effect, a nonperfused lung in vivo. The VO2 was 7.8 ± 1.7 ml/min, and VCO2 was 18.3 ± 1.6 ml/min. The calculated respiratory quotient (RQ) was high (1.97 ± 0.05), especially during zero pulmonary flow, as demonstrated by non-pulsatile pulmonary artery tracing. This may represent the presence of anaerobic metabolism leading to metabolic acidosis and increase in VCO2 from bicarbonate buffering of lactic acid.

## Discussion

Lung transplantation has become a successful therapeutic alternative for selected patients with end-stage lung disease [4]. Despite refinement of the methods of donor

lung procurement and preservation, a number of patients still develop primary severe DLD without any definite causative factor. Five of 83 patients who underwent LTx (5/83 = 6 %) at our institution from 1982 to 1989 died from primary severe DLD, despite maximal conventional support [16]. Haydock and associates at Washington University described 7 of 34 LTx patients (7/34 = 20.6 %) during a 12-month period with DLD; 3 of these patients (3/34 = 9 %) had primary DLD but recovered with conservative measures, probably because of a mild degree of dysfunction [6]. Jurmann and associates in Hannover quote a prevalence of 11.7 % for primary DLD in their experience [7].

In the last 4 years, with new and improved preservation methods [5] and better donor lung selection [15], 8 of 220 patients undergoing LTx (8/220 = 3.6 %) at the University of Pittsburgh suffered from severe primary DLD. All conventional measures failed to stabilize these patients and we proceeded with ECMO support. All ECMO was initiated within 10 h of LTx, and after a mean duration of support of 7 days, seven of the eight patients (87 %) were successfully weaned from it. Bleeding was the most common complication, despite low ACT and minimal heparin infusion. One patient with bilateral single LTx developed ischemic airway injury; the potential anaerobic conditions resulting from high-flow v-a ECMO support may cause ischemic injury to the anastomotic site and may explain this complication.

We routinely use Carmeda Bioactive Surface coated equipment for ECMO. We believe that this system provides an extra dimension of flexibility and safety by allowing one to adjust anticoagulant management, as needed, to fit the clinical need without undue risk of severe hemorrhage.

In conclusion, we believe that in the presence of primary severe DLD, early ( < 12 h) institution of ECMO can be lifesaving. A better understanding of the etiology of primary DLD may help reduce the prevalence of this dreaded complication.

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