CARDIAC AND PULMONARY REPLACEMENT

EXTRACORPOREAL MEMBRANE OXYGENATION AS AN ADJUNCT TREATMENT FOR PRIMARY GRAFT FAILURE IN ADULT LUNG TRANSPLANT RECIPIENTS

Primary graft failure is a catastrophic event in lung transplantation. Failure is characterized by profound abnormalities of gas exchange that are frequently unresponsive to alterations in mechanical ventilation. This condition can be fatal and, if less severe, is usually associated with significant permanent damage to the allograft. We report the use of extracorporeal membrane oxygenation as a means to support lung transplant recipients with severe graft failure. Since 1991, extracorporeal membrane oxygenation has been used on 17 occasions for the temporary support of 16 adult lung transplant recipients. All patients met or exceeded standard National Institutes of Health guidelines for institution of extracorporeal membrane oxygenation. Nine double lung, six single lung, and one heart-lung recipients were supported for 1 to 12 days (mean 4.6 ± 2.2 days). Extracorporeal membrane oxygenation was instituted early, within 7 days of transplantation, in ten patients. Eight early patients (80%) were successfully weaned from extracorporeal membrane oxygenation. Seven of ten (70%) patients were long-term survivors, and five of the seven had normal lung function. In comparison, there were no survivors among six recipients placed on extracorporeal membrane oxygenation for late (≥ 7 days) graft dysfunction. Extracorporeal membrane oxygenation is a lifesaving adjunct in recipients with acute graft failure after lung transplantation. Ischemia-reperfusion injury and acute graft dysfunction after lung transplantation can be successfully reversed with early aggressive intervention. (J THORAC CARDIOVASC SURG 1995;110:723-7)

Lawrence R. Glassman, MD, Robert J. Keenan, MD, M. Charlene Fabrizio, RNCCP, Josh R. Sonett, MD, Morris I. Bierman, MD, Si M. Pham, MD, and Bartley P. Griffith, MD, *Pittsburgh, Pa.*

Extracorporeal membrane oxygenation (ECMO) has been used in the pediatric population with great success. Owing to the pioneering efforts of Bartlett and Gazzaniga¹ and Custer,² success rates of 90% and greater have been achieved. Outcome of adult patients with adult respiratory distress syndrome supported with ECMO has been less favor-

able, with survival rates of 9% to 45%.³⁻⁵ This retrospective report documents the use of ECMO for the support of 16 adult lung transplant recipients from 1991 to 1993. We believe that the success rate in this group of patients should encourage the early use of ECMO, when necessary, in adult lung transplant recipients.

Despite refined preservation techniques and improved early allograft survival, occasional lung transplant recipients have postimplantation graft dysfunction.^{6,7} Primary graft failure, the inability of a pulmonary allograft to sustain ventilation and oxygenation despite full mechanical support, is potentially catastrophic. By offering full pulmonary and in some cases cardiopulmonary support, ECMO provides a means to stabilize the condition of the lung transplant recipient with profound graft dys-

From the Department of Cardiac and Thoracic Surgery, University of Pittsburgh Medical Center, Pittsburgh, Pa.

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Address for reprints: Lawrence R. Glassman, MD, Department of Cardiac and Thoracic Surgery, New York University Medical Center, 530 First Ave., Suite 6-D, New York, NY 10016.

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Table I. Indications for ECMO

	Early (<7 days)	Late (≥ 7 days)
Fio ₂ ≥ 90	10/10	7/7
Static compliance (ml/cm H ₂ O)	3-25 (14)	6.5-16 (12.5)
Shunt fraction (%)	30-80 (40)	25-67 (41)
Inotropic support	10/10	7/7

Values in parentheses are mean values.

function. This stabilization may allow time for allograft recovery or provide a window during which a second graft may be obtained.

Pulmonary failure late after transplantation is often multifactorial. Reversibility is dependent on the nature of the underlying pathologic condition and the extent of the disease. Treatment of the late lung transplant dysfunction group includes early biopsy coupled with aggressive treatment of rejection, infection, and other causative factors. When standard therapy with mechanical ventilation fails, ECMO may be added to the resuscitation algorithm.

Patients and methods

From February 1991 to December 1993 ECMO was required on 17 occasions to support 16 lung transplant recipients with profound graft failure. These 16 patients represent 7.4% of the 215 total patients who underwent transplantation between February 1991 and December 1993. Nine double lung, six single lung, and one heart-lung recipients were supported for 1 to 12 days (mean 4.6 ± 2.2 days). Five patients underwent transplantation for chronic obstructive pulmonary disease, four for pulmonary hypertension, two for cystic fibrosis, two for bronchiectasis, two for pulmonary fibrosis, and one for lymphangiomyomatosis. Graft preservation was accomplished with the combination of prostaglandin E₁ bolus into the donor pulmonary artery followed by hypothermic flush with a modified University of Wisconsin solution (80 to 100 ml/kg). Infusion rates were maintained with the use of a transportable roller pump. Donor lungs were stored in hypothermic preservation solution until implantation. Inflation with 100% oxygen was maintained during the interval from harvest to implantation. Mean ischemic times for the transplanted organs were 293 minutes (range 198 to 392 minutes) for single or first lung and 394 minutes (range 335 to 543 minutes) for the second lung. Double lung transplantations were performed with a bilateral single lung technique. Cardiopulmonary bypass was used in seven of the primary transplant procedures. Four patients in this series underwent retransplantation.

For the purposes of subgroup analysis, we have defined early graft dysfunction as that occurring within the first 7 days of allograft implantation. Any patient placed on ECMO 1 week or longer after transplantation has been placed in the late dysfunction group.

ECMO methodology. When criteria for ECMO were met, a Medtronic Carmeda heparin-bonded system

(Medtronic Cardiopulmonary, Anaheim, Calif.) was used, and initial oxygenation was provided by two parallel Medtronic Maxima hollow-fiber oxygenators. A Bio-Medicus BP-80 centrifugal pump and flow probe (Medtronic Bio-Medicus, Eden Prairie, Minn.) with $\frac{3}{8}$ inch internal diameter $\times$ $\frac{3}{32}$ inch wall thickness heparin-bonded tubing was used. Heparin was administered in the absence of bleeding to maintain a celite activated clotting time of more than 180 seconds (Hemochron activated clotting time sensor, International Technidyne Corporation, Edison, N.J.). Oxygenators were changed only if foaming occurred. If it was necessary to change oxygenators and in the absence of bleeding, Maxima oxygenators (Medtronic) were changed to Avecor silicone rubber membrane systems (No. 3500 Avecor Cardiovascular Inc., Plymouth, Minn.). Heparinization to activated clotting time of more than 200 seconds was achieved. Initial priming was with Plasma-Lyte A solution (Baxter Healthcare Corp., Deerfield, Ill.), which was then displaced with 3 U of bank blood washed with a Cell Saver device (Haemonetics Corp., Braintree, Mass.), 75 mEq sodium bicarbonate, and 500 mg of calcium chloride. Total priming volume was 1800 to 2200 ml. A dual Bird blender (Bird Products Corp., Palm Springs, Calif.) was used to achieve one inspired oxygen fraction (Fio₂) setting. Continuous blood gas monitoring was used routinely in the presence of continuous heparin therapy. Cannulation was performed at the surgeon's discretion by percutaneous or open methods. Carmeda coated cannulas were preferred. Choice of venovenous or venoarterial support was based on hemodynamic stability. Venoarterial support was used at the surgeon's discretion for the more profoundly compromised patients.

Results

We used ECMO on 17 occasions for the temporary support of 16 adult lung transplant recipients. All patients met or exceeded standard National Institutes of Health guidelines for institution of ECMO. ECMO was initiated only when all standard cardiac and respiratory support maneuvers had failed. At the time of ECMO initiation, the arterial oxygen tension/Fio₂ ratio (mean, 58.3 ± 10 , range 32 to 81) was severely depressed. The average alveolar-arterial gradient was widened at 650 mm Hg. As expressed in Table I, ECMO was initiated only when Fio₂ requirements were severely elevated ($\geq 95\%$). Decreased static compliance (≤ 14 ml/cm H₂O) was indicative of severely elevated peak airway pressures despite ventilation with low tidal volumes. Shunt fraction was elevated in all patients ($\geq 40\%$). Although not part of standard National Institutes of Health guidelines, all patients at the time of institution of ECMO also required the use of significant inotropic support. Despite the critical pulmonary and hemodynamic state, overall patient survival was 7 of 16 (48%).

Eight of ten early patients (Table II) (80%) were weaned from ECMO, and seven of ten (70%) were long-term survivors. One of these patients was maintained on ECMO for 3 days as a successful bridge to transplantation. One early patient was weaned from ECMO, underwent retransplantation, and later died after a second period of ECMO support. Five of the seven patients had normal long-term lung function. One patient had an ischemic airway injury after ECMO; this injury was possibly related to venoarterial perfusion in the absence of an intact bronchial circulation.

In contrast to the 70% survivorship of the early group, only two of seven late patients were able to be weaned from ECMO for a brief interval, and none survived hospitalization.

Complications in the 16 patients included episodes of bleeding in four patients, one patient with ischemic airway injury, one patient with renal failure, and one episode of cardiac tamponade requiring drainage.

Discussion

Given the critical pulmonary and hemodynamic state of these patients, we believe ECMO was a lifesaving adjunct. Initiation of ECMO was restricted to patients unable to be supported by conventional means. Application to the subgroup of patients within the first week of transplantation appeared to be most beneficial, with long-term survival of 70%. Potential causes of acute graft dysfunction in this early group include ischemia-reperfusion injury, prolonged preservation time, bleeding with multiple transfusions, cardiopulmonary bypass, circulatory arrest, significant active infection in the native pulmonary bed with release of septic mediators, technical complications, and underlying donor graft disease. We identified no technical complications with graft harvest or preservation in these patients. There does appear to be a reversible component of pulmonary injury which may allow for organ recovery during a period of ECMO support. Continued ventilation with high levels of oxygen and elevated airway pressures does not promote a climate of healing in an already damaged pulmonary bed.

Eight of thirteen patients with venoarterial support and two of four patients with venovenous support were long-term survivors. Because of the small number of patients, we are unable to draw a conclusion as to which form of perfusion is more successful. Our preference is to use venovenous

Table II. ECMO patient characteristics

	Early (<7 days)	Late (≥ 7 days)
Mean age (yr)	43	42
Interval Tx to ECMO (days)	0-6 (1.9)	8-390 (77)
Duration ECMO (days)	1-9 (4)	1-11 (4)
Weaned from ECMO	8/10	2/7
Discharged from hospital	7/10	0/7
Retransplantation	2	2
Survive retransplantation	1	0
VV ECMO	2	2
VA ECMO	8	5

Values in parentheses are mean values. Tx, Transplantation; VV, venovenous; VA, venoarterial.

bypass for those patients who have hemodynamically stable conditions. Venoarterial perfusion is chosen for those patients with profound hemodynamic instability or readily accessible central arterial circulation.

Graft dysfunction may be a critical problem after lung transplantation. Although conservative therapy may suffice, further support may be necessary to allow patients to survive.⁸ In a report by the Washington University group,⁹ donor lung dysfunction occurred in 20% of patients. One of seven patients with early graft dysfunction required retransplantation, and a second was successfully supported for 3 days with ECMO.

In this group of 17 patients, ECMO was more likely to be successful within the first week after transplantation (70% survival) than later (0% survival) after surgery. If the diagnosis of severe post-transplantation lung injury has been established, it appears that ECMO support is potentially lifesaving. Although impossible to prove, early institution of ECMO may alleviate the potential long-term consequences of oxygen toxicity and barotrauma on a newly implanted allograft. ECMO support permits a period of ventilation at lower airway pressures and a decrease in F_{iO_2} , both of which may be beneficial during this critical phase.

The failure of ECMO support to potentiate survival in the late dysfunction group underscores the difficulty of rescuing patients with severe pneumonitis or allograft rejection unresponsive to standard medical therapy.

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Discussion

Dr. Robert M. Kass (*Los Angeles, Calif.*). The use of ECMO as adjunctive therapy for respiratory failure in adult patients has a checkered history. A recent review earlier this year in the *American Journal of Respiratory and Critical Care Medicine* of a randomized clinical trial of ECMO concluded that survival of patients with adult respiratory distress syndrome (ARDS) was not significantly different regardless of whether ECMO was used instead of more traditional therapeutic modalities. The survival in each group was significantly less than 50%.

In the group of patients presented to us here, of those patients placed on ECMO within 7 days of transplantation, seven of ten were long-term survivors and, significantly, five of seven had normal lung function. These results lead to my first question: What do the authors believe is significantly different about the lung transplant recipient versus the group of patients with ARDS that results in improved survival characteristics? Also, a second related question: In what ways did the patients placed on ECMO more than 7 days after transplantation differ from those placed on ECMO earlier?

Dr. Glassman. In regard to the first question, the difference in these patients versus patients with ARDS, I believe that these lungs are generally sound when we harvest and implant them, and we are looking at a severe form of a reperfusion injury perhaps in association with the use of cardiopulmonary bypass and multiple transfusions which accompanied a large number of these cases of early graft failure. These are clearly reversible after support of the patients with ECMO as opposed to support

of patients with ARDS where the origin may be a more long-standing insult to the lung.

The second question was related to the early and late groups. I think the answer is similar; the late groups have either well established infection or well established bad rejection and pneumonitis that is not easily reversible versus an accumulation of perhaps increased pulmonary water with the early group. The support on ECMO allows time for that to come out of the pulmonary bed.

Dr. Kass. The Washington University Lung Transplant Group in St. Louis reported a clinical experience treating seven patients with primary graft dysfunction after lung transplantation in the conventional manner without ECMO. Their overall survival was 100%, with one of the patients requiring retransplantation. How are the authors able to reconcile their use of ECMO when the apparent survival of patients reported by Washington University with primary graft dysfunction is excellent with more traditional therapy?

Dr. Glassman. We have had a number of patients who were not included in this group that I think would fall into the group that was reported from the Washington University group. I think that there are clearly a number of levels of acute graft dysfunction that one can see after lung transplantation and this is in my mind very much the end-stage spectrum of acute graft dysfunction. I am convinced that, with all these patients not only requiring 90% to 100% oxygen but also having high peak airway pressure, poor compliance, and inotropic support, we would not have had a survival rate of 70% in this group without ECMO. Now, it certainly is not a randomized series and I do not believe ethically it would be reasonable to withhold ECMO if you believed that it was an important adjunct for the therapy of these patients, which I believe it is.

Dr. Walter Dembitsky (*San Diego, Calif.*). We have been interested in ECMO support for critically ill patients for some time, and we have begun to relearn some of the lessons of the early ECMO trial. One of them is that prolonged venoarterial bypass can produce stasis thrombosis both in the lungs and in the native ventricle. The question is this: In these two groups that you had, venoarterial versus veno-venous ECMO, were there differences in times of support?

Dr. Glassman. No, there were no differences in times of venoarterial and venovenous support. They were the same, and I think the point you made about thrombosis is an important one. In the absence of bleeding, we anticoagulated the patients to activated clotting times of greater than 180 seconds early on, and in the article I have detailed that we actually anticoagulated them to activated clotting times of 200 to 300 seconds after 48 hours of ECMO support. In the absence of bleeding we believed as well that anticoagulation was important.

Dr. Dembitsky. I think that stasis thrombosis can occur even with pretty fair degrees of anticoagulation, and so I think with the trend in the country being to support patients who are critically ill with peripheral bypass in the venoarterial mode, we are going to be seeing more and more problems related to thrombosis.

Dr. Paul Waters (*Los Angeles, Calif.*). Could you share with us a little about the indications for transplantation in

the group of patients you reported? Was there a predominance of one diagnosis versus another? Was there anything in the preoperative assessment that led you subsequently to notice why they would end up being supported with ECMO and having graft failure?

Dr. Glassman. They were a fairly broad-based group of patients. They included one patient with lymphangioleiomyomatosis, about four patients with chronic obstructive pulmonary disease, and several patients with pulmonary hypertension. In the group who underwent transplantation early, seven of ten patients had cardiopulmonary bypass, indicating that either they had sig-

nificant pulmonary hypertension—one of the patients was a patient with a patent ductus arteriosus who underwent repair with circulatory arrest—or other preoperative factors which would have required cardiopulmonary bypass. There is a report in the last *Journal of Heart and Lung Transplantation* from the Pittsburgh group looking at the incidence of early graft dysfunction with the use of cardiopulmonary bypass and it seems to be somewhat higher. Therefore, I would say that those patients who have increased incidence of cardiopulmonary bypass for lung transplantation may be at higher risk.

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