CARDIOTHORACIC TRANSPLANTATION

SELECTIVE USE OF EXTRACORPOREAL MEMBRANE OXYGENATION IS WARRANTED AFTER LUNG TRANSPLANTATION

Bryan F. Meyers, MD
Thoralf M. Sundt III, MD
Scott Henry, MD
Elbert P. Trulock, MD
Tracey Guthrie, RN
Joel D. Cooper, MD
G. Alexander Patterson, MD

Objectives: Early allograft dysfunction after lung transplantation ranges from subclinical x-ray abnormalities to pulmonary edema, hypoxemia, hypercarbia, and pulmonary hypertension. Management may include extracorporeal circulation to allow recovery of the acute lung injury. We reviewed our experience with extracorporeal membrane oxygenation after lung transplantation to assess the utility of this therapy.

Methods: A retrospective chart review was performed. Single or bilateral lung transplantation was performed in 444 adults from July 1988 to July 1998. Twelve (2.7%) patients experienced allograft dysfunction severe enough to require extracorporeal membrane oxygenation after failure of conventional therapy, including sedation, paralysis, and inhaled nitric oxide.

Results: Seven of 12 patients requiring extracorporeal membrane oxygenation were discharged from the hospital. Mean and median times to extracorporeal membrane oxygenation support were 1.2 days and 0 days, respectively. Mean length of support was 4.2 days. Four patients died while receiving extracorporeal membrane oxygenation support. One patient was weaned from extracorporeal membrane oxygenation but died during the hospitalization. Two patients required acute retransplantation while receiving extracorporeal membrane oxygenation, and one survived to discharge. Three patients continued to receive extracorporeal membrane oxygenation support for more than 4 days, and all 3 died. All survivors had begun receiving extracorporeal membrane oxygenation support by post-transplantation day 1. Three of 7 patients discharged from the hospital died 12 months, 13 months, and 72 months after transplantation because of bronchiolitis obliterans syndrome (n = 2) or lymphoma (n = 1). Four patients are alive 2, 12, 25, and 54 months after transplantation.

Conclusions: Extracorporeal membrane oxygenation provides effective therapy for acute post-transplantation lung dysfunction. The frequency and pattern of our extracorporeal membrane oxygenation use reflects bias toward early extracorporeal membrane oxygenation support for isolated graft failure in otherwise intact and uninfected recipients. (J Thorac Cardiovasc Surg 2000;120:20-8)

From the Divisions of Cardiothoracic Surgery and Pulmonary and Critical Care Medicine, Washington University School of Medicine, St Louis, Mo.

Read at the Twenty-fifth Annual Meeting of The Western Thoracic Surgical Association, Olympic Valley (Lake Tahoe), Calif, June 23-26, 1999.

Received for publication June 29, 1999; revisions requested Sept 7, 1999; revisions received Jan 6, 2000; accepted for publication Jan 11, 2000.

Address for reprints: Bryan F. Meyers, MD, 3108 Queeny Tower, One Barnes-Jewish Hospital Plaza, St Louis, MO 63110-1013 (E-mail: meyersb@msnotes.wustl.edu).

Copyright © 2000 by The American Association for Thoracic Surgery

0022-5223/2000 \$12.00 + 0 12/6/105639

doi:10.1067/mtc.2000.105639

Despite progress in donor lung preservation and surgical technique of lung transplantation, early graft dysfunction remains a major postoperative problem. Estimates of the frequency of this problem range from 15% to 30% of transplant operations. The actual prevalence is difficult to ascertain because the syndrome has been described as multiple entities: reperfusion edema, reimplantation response, primary graft failure, and prolonged postoperative ventilator dependence. The syndrome includes infiltrates on chest radiograph, impairment in oxygenation, and graft biopsy histology of diffuse alveolar damage. The severity ranges from a trivial subclinical radiographic finding to full-blown adult respiratory distress syndrome. The pathophysiology involves a combination of increased permeability of the pulmonary capillary bed and increased pulmonary vascular resistance leading to transient pulmonary hypertension. Rejection, bacterial pneumonia, cytomegalovirus pneumonitis, and pulmonary venous obstruction can mimic the syndrome.

Standard treatment in moderate and severe cases includes vigorous diuresis and extended support with positive-pressure ventilation. Sedation and paralysis are typically used to improve the efficiency of the ventilator and decrease oxygen consumption. We previously reported that inhaled nitric oxide improves gas exchange in patients with severe early allograft dysfunction.¹ In very severe cases extracorporeal membrane oxygenation (ECMO) has been necessary to support gas exchange until the recovery of the lungs. We retrospectively reviewed our use of ECMO in the setting of postoperative lung dysfunction after lung transplantation to assess the likelihood of success of this salvage therapy as measured by weaning from ECMO, discharge from the hospital, and eventual long-term survival. We also sought to identify characteristics of successful and unsuccessful uses of post-transplantation ECMO to guide future use of this therapy.

Patients and methods

A retrospective chart review was performed. Single or bilateral lung transplantation was performed in 444 adults from July 1988 to July 1998. Twelve (2.7%) patients experienced allograft dysfunction severe enough to require ECMO after failure of conventional therapy, including sedation, paralysis, and inhaled nitric oxide. The decision to use ECMO was made by the surgeon in the 6 patients requiring ECMO on the day of surgery. In the remaining 6 patients ECMO was used after the joint determination by the surgeon and the transplant pulmonologist that conventional management was failing. Ten patients had received bilateral transplants, and two had received single lung transplants. Table I contains the graft ischemic times and cardiopulmonary bypass (CPB) times for these patients. Reperfusion injury is the most prevalent reason

for immediate and early lung dysfunction, but not all of the patients in this report could be described as fitting that diagnosis. The first patient in this series began receiving ECMO for hypotension and hemodynamic instability that was otherwise unmanageable with pressors. The third patient in the series underwent a cardiovascular collapse on weaning from CPB. The failure to wean was eventually attributed to a technically unacceptable pulmonary venous anastomosis. All other patients began receiving ECMO for the characteristic picture of reperfusion injury and primary graft dysfunction: hypoxemia, hypercarbia, acidosis, increased pulmonary arterial pressures, and decreased ventilatory compliance of the lungs. The most recently treated patient fit the profile for reperfusion injury, but a diligent search for technical errors identified a pressure gradient across a pulmonary artery anastomosis that was subsequently revised on ECMO support.

Operative techniques. In all cases venoarterial ECMO support was provided. In the first 3 patients treated in this manner, we performed the ECMO cannulation by means of femoral artery and femoral vein cannulations. In 8 of the subsequent 9 patients, we avoided groin cannulation and chose to cannulate the ascending aorta and the right atrium directly. The oxygenator used for the ECMO circuit was a silicone rubber membrane model #I 4500-2A from Avecor (Plymouth, Minn), and the pump was a centrifugal blood pump from Medtronic Inc (Eden Prairie, Minn).

Conduct of ECMO. Most patients were moderately or severely coagulopathic at the time of cannulation. Heparin was therefore typically withheld for 12 to 24 hours to allow correction of the coagulopathy. Heparin infusion was then titrated to maintain an activated clotting time of 180 to 250 seconds. Special care was given to ensure adequate heparinization during the weaning from ECMO. ECMO flows were typically 2.5 to 3.5 L/min. All patients had pulmonary arterial catheters, and ECMO flows were titrated to ensure evidence of right ventricle ejection as measured by systolic peaks on the pulmonary artery catheter. Once ECMO had been established, we decreased the rate and tidal volume of the ventilator to minimize barotrauma but maintain moderate levels (10-15 cm H₂O) of end-expiratory pressure. The decision to wean from ECMO was based on the appearance of the lungs on chest x-ray film and the response of the patient's oxygenation, ventilation, airway pressures, and pulmonary artery pressures to lower ECMO flow rates and resumption of standard ventilator settings.

Statistical methods. Continuous data are described by use of mean values $\pm$ 1 SD. A 2-sample *t* test with Bonferroni correction was used to compare ischemic times of ECMO and non-ECMO transplant recipients. The Fisher exact test was used to analyze the frequency of ECMO use in subgroups of our entire transplant population sorted by sex, diagnosis, and type of transplant (single vs bilateral). A paired *t* test was used to compare blood gas results and pulmonary pressures before and after the start of ECMO support. A logistic regression was used in an attempt to identify statistically significant risk factors in the 12 patients receiving ECMO when compared with the 432 patients undergoing transplantation without subsequent need for postoperative ECMO.

Table I. General characteristics of patients treated with ECMO

Patient	Sex	Diagnosis	Transplant type	Ischemic time, first graft (min)	Ischemic time, second graft (min)	CPB time (min)
1	F	PH	Single	480	NA	211
2	F	CF	Bilateral	300	523	315
3	F	PH	Single	275	NA	297
4	F	CF	Bilateral	330	480	104
5	F	PH	Bilateral	265	310	267
6	F	PH	Bilateral	270	300	280
7	F	Sarcoidosis	Bilateral	198	310	99
8	F	PH	Bilateral	290	315	269
9	F	Bronchiectasis	Bilateral	257	511	204
10	M	IPF	Bilateral	307	363	None
11	F	CF	Bilateral	330	330	197
12	F	COPD	Bilateral	314	464	None

PH, Pulmonary hypertension; NA, not applicable; CF, cystic fibrosis; IPF, idiopathic pulmonary fibrosis; COPD, chronic obstructive pulmonary disease.

Results

We have used ECMO in 12 lung recipients since the inception of the lung transplant program at Washington University. Clinical data recorded on these patients are summarized in Table I. The patients requiring ECMO included 11 women and 1 man out of an overall population of transplant recipients including 225 women and 219 men. The mean age was 38 ± 11 years. The mean ischemic time to the first lung was 301 ± 67 minutes, and the mean ischemic time to the second lung (in the 9 bilateral transplants) was 390 ± 92 minutes. These times were not significantly different from ischemic times for our transplant recipients as a whole: 283 ± 77 minutes for the first lung ($P = .74$) and 328 ± 98 minutes for the second lung ($P = .13$). Ten of the 12 patients underwent bilateral transplants. The underlying diagnoses leading to transplantation included pulmonary hypertension in 5 patients, cystic fibrosis in 3 patients, and emphysema, pulmonary fibrosis, sarcoidosis, and bronchiectasis in 1 patient each. The prevalence of ECMO use in patients with pulmonary hypertension (5/51 [9.8%]) was higher than the prevalence in patients with other diagnoses (7/293 [1.8%]). All patients had been stable outpatients until the day of transplantation.

The initiation of ECMO support took place on the day of surgery in 6 patients, on postoperative day 1 in 4 patients, and on postoperative days 2 and 8 in 1 patient each. The 6 patients receiving ECMO on the day of surgery included 4 who began receiving ECMO in the same operation as the transplant and 2 who had brief trials of conventional ventilator and pharmacologic support in the intensive care unit before returning to the operating room for cannula-

tion. ECMO support was continued for a time period ranging from 1 to 10 days, with a mean of 3.6 ± 2.9 days.

The goal of ECMO in this situation is to maintain adequate oxygenation and ventilation, decrease pulmonary artery pressures to decrease the transcapillary gradient in the pulmonary vasculature, and allow reduction in the rate and tidal volume of mechanical ventilation to limit secondary ventilator-induced barotrauma. Table II contains the blood gas results, airway pressures, and mean pulmonary arterial pressures for these patients at the time of ECMO cannulation and 4 hours after the initiation of ECMO support. The arterial pH improved from 7.29 ± 0.11 to 7.39 ± 0.07 ($P = .005$) in the first 4 hours of ECMO. Similarly, the PO_2 increased from 52.2 ± 8.4 to 231 ± 78.4 ($P = .001$), and the PCO_2 fell from 46.3 ± 11.8 to 33.9 ± 3.6 ($P = .003$). The peak inspiratory pressures fell from 63.3 ± 14.7 cm H_2O to 37 ± 4.0 cm H_2O ($P = .001$). Mean pulmonary artery pressures fell from 39.2 ± 8.9 mm Hg to 18.5 ± 6.8 mm Hg ($P = .001$). The fraction of inspired oxygen was reduced from a mean of 1.00 ± 0.0 to 59.2 ± 21.9 in the 4 hours after ECMO cannulation ($P = .001$).

Complications experienced during or after ECMO support are summarized in Table III. Ten patients had notable postoperative bleeding with multiple transfusions. Seven patients required re-exploration specifically for bleeding. Renal failure developed in 7 patients to the extent that temporary dialysis or ultrafiltration was required. Four patients were noted to have neurologic injury of some kind, 2 who subsequently recovered completely and 2 with massive strokes, which led to decisions to terminate further support.

Table II. Response of physiologic profile to ECMO support

	Pre-ECMO	4 hours of ECMO	P value
pH	7.29 ± 0.11	7.39 ± 0.07	.005
Po ₂ (mm Hg)	52.2 ± 8.4	230 ± 78	.001
Pco ₂ (mm Hg)	46.3 ± 11.8	33.9 ± 3.6	.001
FiO ₂ (%)	100 ± 0	59.2 ± 21.9	.001
PIP (cm H ₂ O)	63.3 ± 14.7	37.4 ± 4.0	.001
PAP (mm Hg)	39.2 ± 8.9	18.5 ± 6.8	.001

FiO₂, Fraction of inspired oxygen; PIP, peak inspiratory pressure; PAP, pulmonary arterial pressure.

The overall survival results of our experience with ECMO support after lung transplantation is recorded in Table IV and includes 7 patients who survived to be discharged from the hospital and 5 patients who died during the postoperative hospitalization. Of the 5 patients who died, 4 died when all support, including ECMO, was withdrawn after a consensus was reached by the team of physicians and each patient's family that irreversible multisystem organ failure had made the situation hopeless for recovery. One patient was successfully weaned from the ECMO circuit only to die several weeks later of anoxic encephalopathy, acute renal failure, and *Pseudomonas* species sepsis.

A logistic regression was used to determine whether patient characteristics could define a subgroup of patients at statistically increased risk for graft failure requiring ECMO. The ability to make these inferences is limited by several factors: One was the small number of patients receiving ECMO (n = 12) versus patients not receiving ECMO (n = 432). Also, the coarse binary nature of the response variable (ECMO vs non-ECMO) further limits the leverage of statistical procedures in these patients. The studied variables included ischemic time, transplant type (single vs bilateral), recipient diagnosis, donor quality (ideal or marginal), age, sex, CPB time, and preoperative mechanical ventilation (yes or no). When the variables are considered alone, age, sex, recipient diagnosis, and CPB time were all significant factors as recorded in Table V. Several multivariate models were then constructed in an attempt to identify important variables that identify patients at higher risk for requiring postoperative ECMO support. None of these models had the sensitivity or specificity to adequately discriminate between the patients receiving and not receiving ECMO, and as a result, the conclusion was made that the data do not offer adequate information to assess ECMO risk factors.

One statistical model looked only at women who had received bilateral transplants. This group included 9

Table III. Complications of ECMO support

ECMO complications	Patients, n (%)
Coagulopathy, multiple transfusions	10 (83)
Re-exploration for bleeding	7 (58)
Renal failure requiring support	7 (58)
Stroke	3 (25)
Arterial injury at cannulation site	1 (8)
Other	3 (25%)

patients receiving ECMO and 122 patients not receiving ECMO. When variables were evaluated separately, the following factors were significant in identifying patients receiving ECMO: ischemic time ($P = .02$), diagnosis of pulmonary hypertension ($P = .036$), and use of CPB ($P = .005$). Two joint models were evaluated, one using CPB and one omitting CPB on the grounds that its use was influenced by lung failure leading to ECMO, and it was thus artifactually linked to ECMO. In the joint model without CPB considered, ischemic time ($P = .006$) and diagnosis of pulmonary hypertension ($P = .014$) were significant. In the model using CPB as a variable, only ischemic time ($P = .007$) and CPB use ($P = .008$) were significant.

Discussion

Our experience and that described by others suggest that there is a definite role for ECMO in treating acute donor lung dysfunction. In the most favorable scenario, acute postoperative graft dysfunction begins almost immediately and presents as pulmonary edema with hypoxemia and noncompliant lungs. This immediate dysfunction is almost always reversible, and ECMO support is advisable when conventional ventilatory strategies prove inadequate. Indeed, an argument can be made for the use of ECMO early in the course of a rapidly evolving reperfusion injury, rather than as a last-ditch heroic maneuver to salvage what may, by that time, be an irreversible lung injury. In most cases the graft lung will heal and the pulmonary edema will resolve, allowing for improved oxygenation and ventilation within 1 to 5 days. The use of ECMO is associated with substantial risk, and there is a high morbidity and mortality in the patients treated in this manner.

The pattern of use of ECMO described in this report is conservative compared with that seen in reports from other centers. To better understand our own habits in using ECMO, we reviewed the hospital charts of the 2 patients in our transplant database who died of primary

Table IV. Result of ECMO on lung recovery and patient survival

Patient	ECMO start	ECMO days	Weaned	Outcome	Comment
1	0	3	Yes	Lived	
2	1	1	Yes	Lived	
3	0	4	Yes	Died	Weaned but died 4 weeks later; brain death
4	0	3	Yes	Lived	
5	0	4	Yes	Lived	
6	1	10	No	Died	Failure to improve; support withdrawn
7	2	10	No	Died	Massive hemorrhage
8	8	1	No	Died	Brain death
9	1	1	Yes	Lived	Successful retransplant
10	1	8	No	Died	Failed retransplant
11	0	4	Yes	Lived	
12	0	1	Yes	Lived	

ECMO start, Days elapsed between lung transplant and ECMO cannulation; ECMO days, length of ECMO support; weaned, removed from ECMO circuit before death.

Table V. Univariate analysis of risk factors for ECMO use

Variable	χ^2	P > χ^2
Ischemic time	2.77	.096
Recipient age	4.51	.034
Donor PO ₂	0.29	.6
Donor quality	0.07	.8
Vented	0.39	.54
Single versus bilateral	0.82	.37
CPB time	12.06	.0005
Sex	5.19	.023
Pulmonary hypertension	4.4	.036

Donor PO₂, Partial pressure of oxygen in donor under standard conditions of 100% inspired oxygen and 5 cm H₂O end-expiratory pressure.

graft failure without the use of ECMO. These patients are mentioned to emphasize our own selectivity of ECMO use and not to suggest that their outcome might have improved with the use of ECMO. One man had a stormy postoperative course after a bilateral transplant for idiopathic pulmonary fibrosis. He underwent an episode of ischemic colitis leading to colectomy on postoperative day 14 and had persistent pulmonary dysfunction and pulmonary hypertension. He died of a massive endobronchial hemorrhage on postoperative day 38, and the cause of death was determined to be diffuse alveolar damage with acute hemorrhage. The other patient was a woman with primary pulmonary hypertension who underwent single-lung transplantation and closure of a patent foramen ovale by means of a median sternotomy. She did poorly from the start, with severe pulmonary hypertension, right ventricular dysfunction, poor gas exchange, and hypotension necessitating high-dose pressors. She later had renal and hepatic failure, as well as thrombocytopenia. Because of her multiorgan dysfunction, we declared

that ECMO was not indicated, and she died on postoperative day 8.

The prevalence of women in this group of patients requiring ECMO is difficult to explain. Eleven of the 12 patients described in this report are women, yet the overall population of lung transplant recipients in our institution is very evenly distributed according to sex: 219 men and 224 women at a recent count. It is quite possible that either the smaller size of the female recipient or the smaller size of the graft lung make preservation of the lung more difficult. In particular, our habit of using iced laparotomy sponges around the lung as it is implanted is made more difficult when the pleural space is small. This problem was specifically mentioned in at least one operative note of a patient who eventually required ECMO. Also, the smaller size of the pulmonary vessels being anastomosed decreases the tolerance for technical error. Finally, patients with a diagnosis of primary or secondary pulmonary hypertension are represented out of proportion to their prevalence in our entire transplant experience, and the majority of these patients are women.

For those patients receiving ECMO, the prevalence of female sex is in part dependent on the recipient diagnosis of pulmonary hypertension. This problem is representative of multiple codependencies seen in the data collected on these patients. For instance, patients undergoing transplantation with CPB who are in good physiologic condition will be removed from the CPB support very quickly after reperfusion of the graft lung or lungs. If these patients are acutely unstable and require ECMO, the CPB support will be extended until an ECMO circuit is prepared and inserted into the perfusion system. Thus the patients receiving ECMO will have longer bypass runs than patients not receiving ECMO, but it is misleading to conclude that the longer

bypass run caused the need for the ECMO support. Similarly, in a bilateral transplant started without bypass, immediate dysfunction of the first transplanted lung will cause an interruption in the flow of the operation to cannulate for bypass. This will prolong the ischemic time for the second lung. If this patient later requires ECMO, the longer ischemic time may be viewed as a partial cause of the need for ECMO, when in fact the long ischemic time is a result of the immediate dysfunction of the first lung. Finally, patients with some diagnoses (cystic fibrosis and pulmonary hypertension) tend to be much younger than patients with other diagnoses (idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease), and this partial dependency of age on diagnosis will cloud conclusions about the role of recipient age on the subsequent risk for ECMO support.

With regard to technical considerations, our preferred ECMO cannulation sites are the ascending aorta and right atrium, whereas others have advocated a femoral arterial and venous cannulation. The main putative benefit of femoral cannulation is avoidance of a thoracotomy for the insertion and subsequent removal of the ECMO circuit. Because the majority of our patients have required re-exploration of the chest to evacuate blood and search for bleeding sites, this potential benefit is minimized. Furthermore, the majority of our patients (11/12) have been women, and the smaller size of the femoral vessels increases the likelihood of complications of a groin cannulation. We had one such complication and have subsequently chosen to use thoracic cannulation whenever possible. A more unusual complication of femoral ECMO has been reported by others in which the lower half of the body receives the well-oxygenated ECMO blood while the upper half of the body receives the poorly oxygenated blood leaving the lungs.² A phenomenon such as this cannot occur with thoracic cannulation.

Early lung dysfunction after transplantation remains a problem despite continued progress in graft preservation. Standard therapy, consisting of mechanical ventilatory support and pharmacologic reduction of pulmonary arterial pressures, is based on the knowledge that most cases of reperfusion injury are transient and completely reversible. The drawback of standard therapy is that stiff edematous lungs require high drive pressures for ventilation, and this inevitably leads to a secondary barotrauma superimposed on the primary graft dysfunction. Additionally, the alprostadil (prostaglandin E₁) used to decrease the pulmonary artery pressures inevitably causes varying degrees of systemic hypotension. The goal of ECMO is to assist with gas

exchange and systemic perfusion while allowing the lungs to heal without the additional injury caused by the ventilator.

Since the first report of combined therapy with ECMO support with lung transplantation in 1978, these two therapies for lung failure have been combined in every way imaginable. Several authors have reported use of ECMO to support pretransplant patients until a graft is available. In some cases ECMO provides a direct bridge to transplantation, but in several patients the ECMO was used for a brief period of acute exacerbation of the lung failure and was not needed right up to the time of transplantation.³⁻⁹

The most common pairing of lung transplantation and ECMO is the scenario described by our experience in this article: the support of a post-transplant recipient during an episode of reversible acute lung dysfunction.^{3,4,6,10-19} In some instances it becomes apparent that the acute post-transplant lung dysfunction may not be reversible. In these rare cases the goal of ECMO changes and becomes support of post-transplant recipient until retransplantation is performed. Another distinct pattern of ECMO use after transplantation is the support of a post-transplant recipient during late lung dysfunction. This category is subjective, and the transition from early to late lung dysfunction varies according to authors' whims. Some authors have considered acute lung injury to include the need for ECMO within 48 hours of transplantation, with subacute and late failure being defined as 2 to 7 days and more than 7 days, respectively.¹⁰ Others have declared *early* lung dysfunction to mean less than 7 days after transplantation and *late* dysfunction to mean 7 days or more after transplantation.¹¹ The final and most unusual combination of ECMO and transplantation is the prophylactic support of a transplant recipient to prevent acute lung dysfunction.²⁰ The single cited case report describes the authors' desire to minimize the likelihood of life-threatening reperfusion injury by performing the transplant on ECMO and keeping the patient supported with ECMO for several days postoperatively until the early risk of reperfusion edema has passed.

Eriksson and Steen²¹ have reported a novel therapeutic approach to life-threatening dysfunction of the newly transplanted lung. They reported 2 cases in which primary graft failure, with a severity meeting their criteria for institution of ECMO, was managed with induced hypothermia, sedation, muscle relaxation, steroids, and isotonic buffers to stabilize the patients and reduce their metabolic activity. Both patients survived without ECMO or retransplantation. In the absence of novel strategies such as this one, the only

alternatives for severe early lung dysfunction after transplantation are conventional ventilation and pharmacologic manipulation of pulmonary artery pressures or ECMO.

Conclusions

We conclude that ECMO support in the setting of acute post-transplantation pulmonary failure is reasonable therapy with an acceptable likelihood of success. Extracorporeal support allows normal gas exchange and an immediate reduction in peak airway pressure and pulmonary artery pressure and thereby minimizes additional reperfusion pulmonary edema and secondary barotrauma. The highest likelihood of success will be in patients with a technically sound operation in whom reperfusion injury is identified immediately and treated with ECMO without delay. Extracorporeal support is associated with a high risk of renal and neurologic impairment, which limits its attractiveness as a therapy for less severe reperfusion injury. Patients with delayed failure of the transplanted lung have more complex disease and are less likely to have the predictable favorable response to ECMO.

We gratefully acknowledge the help of Richard B. Schuessler, PhD, Kathryn Trinkaus, and Paul Thompson, PhD, for their assistance with the statistical analysis.

REFERENCES

1. Date H, Triantafyllou A, Trulock E, Cooper J, Patterson G. Inhaled nitric oxide reduces human lung allograft dysfunction. *J Thorac Cardiovasc Surg* 1996;111:913-9.
2. Sekela ME, Noon GP, Holland VA, Lawrence EC. Differential perfusion: potential complication of femoral-femoral bypass during single lung transplantation. *J Heart Lung Transplant* 1991;10:322-4.
3. Nelems JM, Duffin J, Glynn MFX, Brebner J, Scott AA, Cooper JD. Extracorporeal membrane oxygenator support for human lung transplantation. *J Thorac Cardiovasc Surg* 1978;76:28-32.
4. Saunders NR, Alpert HM, Cooper JD. Sequential bilateral lung transplantation for paraquat poisoning. *J Thorac Cardiovasc Surg* 1985;89:734-42.
5. Van Meurs KP, Rhine WD, Benitz WE, et al. Lobar lung transplantation as a treatment for congenital diaphragmatic hernia. *J Pediatr Surg* 1994;29:1557-60.
6. Bridges ND, Mallory GB, Huddleston CB, Canter CE, Sweet SC, Spray TL. Lung transplantation in children and young adults with cardiovascular disease. *Ann Thorac Surg* 1995;59:813-21.
7. Demertzis S, Haverich A, Ziemer G, et al. Successful lung transplantation for posttraumatic adult respiratory distress syndrome after extracorporeal membrane oxygenation support. *J Heart Lung Transplant* 1992;11:1005-7.
8. Jurmann MJ, Haverich A, Demertzis S, Schaefer HJ, Wagner TO, Borst HG. Extracorporeal membrane oxygenation as a bridge to lung transplantation. *Eur J Cardiothorac Surg* 1991;5:94-7.
9. Jurmann MJ, Haverich A, Demertzis S, et al. Extracorporeal membrane oxygenation (ECMO): extended indications for artificial support of both heart and lungs. *Int J Artif Organs* 1991;14:771-4.
10. Whyte RI, Deeb M, McCurry KR, Anderson HL, Bolling SF, Bartlett RH. Extracorporeal life support after heart or lung transplantation. *Ann Thorac Surg* 1994;58:754-9.
11. Glassman LR, Keenan RJ, Fabrizio MC, et al. Extracorporeal membrane oxygenation as an adjunct treatment for primary graft failure in adult lung transplant recipients. *J Thorac Cardiovasc Surg* 1995;110:723-6.
12. Zenati M, Pham SM, Keenan RJ, Griffith BP. Extracorporeal membrane oxygenation for lung transplant recipients with primary severe donor lung dysfunction. *Transplant Int* 1996;9:227-30.
13. Ball JW, Noon GP, Short HD, Scheinin SA. Extracorporeal membrane oxygenation for early graft dysfunction in lung transplantation: a case report. *J Heart Lung Transplant* 1997;16:468-71.
14. Haydock DA, Trulock EP, Kaiser LR, Knight SR, Pasque MK, Cooper JD. Management of dysfunction in the transplanted lung: experience with 7 clinical cases. *Ann Thorac Surg* 1992;53:635-41.
15. Badesch DB, Zamora MR, Jones S, Campbell DW, Fullerton DA. Independent ventilation and ECMO for severe unilateral pulmonary edema after SLT for primary pulmonary hypertension. *Chest* 1995;107:1766-70.
16. Tamez A, Cooper DK, Novitzky D, Chaffin JS, Greer AE, Zuhdi N. Experience with cardiorepiratory support devices in patients undergoing heart and heart-lung transplantation. *J Okla State Med Assoc* 1990;83:449-53.
17. Nguyen DQ, Kulick DM, Bolman RM, Park SJ. Temporary ECMO support following lung and heart-lung transplantation [abstract]. *J Heart Lung Transplant* 1999;18:55.
18. Jurmann MJ, Schaefer HJ, Demertzis S, Haverich A, Wahlers T, Borst HG. Emergency lung transplantation after extracorporeal membrane oxygenation. *ASAIO J* 1993;39:M448-52.
19. Haverich A, Hirt S, Wahlers T, Schaefer H-J, Zink C, Borst H-G. Functional results after lung retransplantation. *J Heart Lung Transplant* 1994;13:48-55.
20. Chan CY, Chen YS, Ko WJ, et al. Extracorporeal membrane oxygenation support for single lung transplantation in a patient with primary pulmonary hypertension. *J Heart Lung Transplant* 1998;17:325-7.
21. Eriksson LT, Steen S. Induced hypothermia in critical respiratory failure after lung transplantation. *Ann Thorac Surg* 1998;65:827-9.

Discussion

Dr Frederick Grover (*Denver, Colo*). This article reviews the Washington University Barnes Hospital experience for the use of ECMO for end-stage pulmonary graft failure after lung transplantation. Of the 444 lung transplants performed during the 10-year period, 2.7% or 12 patients required ECMO for allograft dysfunction that defied conventional therapy. Seven of these 12 patients survived. This is a very good survival figure for this desperately ill group of patients who otherwise very likely would not have survived without the use of ECMO. Of particular interest is the fact that 10 of 12 had a bilateral sequential transplant, 11 of the 12 were women, and 5 underwent transplantation because of pulmonary hypertension. Very good results were seen in terms of

the physiologic improvement of these patients. As you mentioned, this is a high-morbidity procedure with bleeding, renal dysfunction, and a high incidence of stroke and irreversible brain damage.

Our experience at the University of Colorado is very similar. We are also conservative in the use of ECMO and use many of your indications. Our use of this in 138 transplants we performed over the last 8 years is 2.2% compared with your 2.7%. Actually, of the 3 in which we used ECMO, 1 patient had an acute myocardial infarction; therefore, we had 2 with graft failure. One of our 2 patients is alive and well 6 years after the operation. Therefore, it is a useful procedure in many of our hands.

I have several questions for Dr Meyers and his group. The incidence of female sex and pulmonary hypertension in your ECMO group was significantly greater than that found in your transplant population as a whole, which you demonstrated. Have you done a multivariate analysis to separate out whether these are both independent risk factors because the 5 patients with persistent pulmonary hypertension were all women?

Dr Meyers. No I have not, although I think we will have to do that. It is worrisome that 11 of the 12 were women and that all 5 pulmonary hypertensive patients were women; therefore, a multivariate analysis will be necessary to dissect out which is the leading cause. The patients with pulmonary hypertension and the women do share a characteristic that might lead to inadequate preservation of the lung, even if the ischemic times are not significantly longer. Our personal technique of keeping the donor lung cool during implantation depends on placement of iced lap pads around the graft lung as it is being implanted. Patients with a large chest volume relative to the volume of the implanted lung allow us a much better ability to keep the graft cold while it is being implanted. I think women and pulmonary hypertensive patients tend to have small chest volumes in relation to the size of the lung being implanted. They may share this characteristic, but it will take multivariate analysis to distinguish the leading risk factor.

Dr Grover. Although your analysis showed that the ischemic times of your ECMO group were not statistically significantly longer than those of your population as a whole, they were longer nevertheless. I think the second lung in your bilateral sequential group had an average ischemic time of 1 hour longer in your ECMO group compared with your group as a whole, and there were 4 patients who had ischemic times of greater than 8 hours. Therefore, because this is a relatively rare event and your numbers are relatively small, do you think that the trend is there, even though findings were statistically insignificant in this area? Do you think that ischemic time probably is indeed a predictor of this?

Dr Meyers. I would agree. I think that there is a trend, and if more patients had required ECMO, it might have fallen out as being significant. I also noticed that the difference in the ischemic time for the first lung was much smaller than that for the second lung, and many of these patients actually had problems on implantation of the first lung. The delay in

implanting the second lung was often cannulation for bypass and trying to correct that problem with the first one. The longer ischemic time on the second lung is skewed a bit by the fact that problems have already arisen, and much of that time is cold ischemic time, which does not greatly affect function.

Dr Grover. That may lead into my final question, which concerns the potential effect of CPB on lung dysfunction. CPB was used in 10 of your 12 patients, and obviously 5 of those had persistent pulmonary hypertension. Therefore, I think all of us would use bypass in those individuals, but in 4 it exceeded 8 hours. Maybe this is a question of what goes first, the horse or the cart, but we have found an association in our experience in Denver with the use of CPB and lung dysfunction. Have you analyzed the data in this regard?

Dr Meyers. No, I have not. You mentioned the 8-hour time frame. I think there were a couple of ischemic times that ran 8 hours. The range of time for CPB went from 99 minutes for the shortest bypass run to 315 minutes. The latter is a pretty substantial bypass run. When I take the next step with the multivariate analysis, the use of CPB will be included in the analysis. Our overall rate of use of CPB is about 25% for the entire cohort. Therefore, certainly 10 of 12 is an overrepresentation. Again, when the patients are having difficulty with pulmonary edema and poor oxygenation immediately after the first lung is unclamped, a response in many cases is to begin CPB. In those cases the dysfunction leads to CPB rather than the other way around, as you postulate.

Dr Richard Whyte (Stanford, Calif). A few years ago, back in Michigan, we looked at a similar group of patients who required ECMO support after heart and lung transplantation. In those patients undergoing lung transplantation, we did not have the benefit of nitric oxide. Do you think that nitric oxide has decreased the need for ECMO, particularly in your patients requiring single-lung transplantation?

Dr Meyers. We started using nitric oxide in 1994, and therefore the last 6 of the 12 patients had the benefit of nitric oxide. It is hard to know which component of the overall care has led to a gradual decrease in the frequency. When I look back, there has been approximately one patient per year over the 10 years, with the exception of 1996, yet the volume of transplants each year has increased. Therefore, the frequency has decreased over time. Nitric oxide certainly has been one component of that decrease. Other work by Drs Patterson and Cooper and the rest of our group has shown that nitric oxide can help either mitigate or eliminate early lung dysfunction. Nitric oxide probably played a role, but it is difficult to know what role it did play and what other improvements in the process contributed to the falling incidence of ECMO use.

Dr Whyte. You have clearly shown that the outcome in these patients who require ECMO is not very good overall. These patients are critically ill, but you certainly showed that some of these patients who otherwise would die can be salvaged with this technique.

Dr Joseph Arcidi (Salt Lake City, Utah). Having participated in this experience, I know that the philosophy of transplantation for pulmonary hypertension at Washington

University has sometimes favored single-lung transplantation and sometimes favored bilateral transplantation. Has the frequency with which you perform bilateral transplantation for pulmonary hypertension affected the incidence of requiring ECMO or nitric oxide for support of those patients with lung dysfunction afterward?

Dr Meyers. With regard to the use of nitric oxide: we start all patients on it after transplantation. We bring it into the operating room, and if it is a bilateral transplant, we start it running when we start perfusing the first graft. When we get to the intensive care unit, if the pulmonary function is good and the pulmonary artery pressures are low, we wean it off fairly rapidly. The focus of questions today on the pulmonary hypertensive patients is expected on the basis of their relative frequency in this group. Unfortunately, or fortunately, they are not being referred for transplantation anymore. In the

early years of this experience, they made up probably 20% of all patients on whom we performed transplantation. Now the percentage is probably about 5%. As a result, 5 of the first 6 patients in this experience had pulmonary hypertension, and only 1 of the last 6 had pulmonary hypertension. When they do undergo transplantation, our tendency now is to opt for bilateral transplantation.

Dr Arcidi. Is it possible to separate out the causes of stroke and renal failure from ECMO or the insult before instituting ECMO in these patients?

Dr Meyers. I do not know. Of the patients who eventually were found to have strokes, none had a period of lucency during which we could demonstrate that they made it through the transplant neurologically intact and the injury was inflicted by ECMO. They basically never regained consciousness to any certain extent after the transplant.

ON THE MOVE?

Send us your new address at least six weeks ahead

Don't miss a single issue of the journal! To ensure prompt service when you change your address, please photocopy and complete the form below.

Please send your change of address notification at least six weeks before your move to ensure continued service. We regret we cannot guarantee replacement of issues missed due to late notification.

JOURNAL TITLE:

Fill in the title of the journal here. _____

OLD ADDRESS:

Affix the address label from a recent issue of the journal here.

NEW ADDRESS:

Clearly print your new address here.

Name _____

Address _____

City/State/ZIP _____

COPY AND MAIL THIS FORM TO:

Mosby
Subscription Customer Service
6277 Sea Harbor Dr
Orlando, FL 32887

OR FAX TO:

407-363-9661

Mosby

OR PHONE:

800-654-2452
Outside the U.S., call
407-345-4000