Extended use of extracorporeal membrane oxygenation after lung transplantation

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Objectives: Extracorporeal membrane oxygenation (ECMO) for severe graft failure after lung transplantation is accepted immediately postoperatively; extending its use is controversial. We evaluated our post-lung transplant ECMO experience, which included extended indication, to (1) determine its prevalence, risk factors, indications, and timing, (2) compare complications and outcomes of these patients with those not requiring it, and (3) identify risk factors, including indications, for mortality.

Methods: From February 1990 to October 2005, 474 patients underwent lung transplantation; postoperative ECMO support was instituted for severe graft failure 23 times in 22 patients (4.0%). Indications for ECMO and its timing were obtained by reviewing medical records and survival by systematic follow-up.

Results: No factor evaluated predicted severe graft failure leading to ECMO. The most common indication for ECMO was early graft failure (13 patients); however, it was also used for pneumonia or sepsis (6) and acute rejection (4). ECMO was initiated at a median arterial oxygen tension/inspired oxygen fraction of 59 at a median of 2 days postoperatively and was maintained for a median of 4 days. The most common complications were renal failure (57%) and bleeding (43%). ECMO was effective in salvaging patients with rejection and early graft failure (survival at 1, 3, 6, and 12 months: 62%, 54%, 49%, and 41%), but ineffective for pneumonia or sepsis (survival at these intervals: 9%, 4%, 4%, and 3%).

Conclusions: ECMO can be extended beyond early severe graft failure to acute rejection and can be considered after the immediate postoperative period. Survival after ECMO in patients with pneumonia or sepsis is poor.

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Severe graft failure, characterized by impaired gas exchange, is uncommon after lung transplantation but carries high mortality.¹ Extracorporeal membrane oxygenation (ECMO) may be necessary to provide lifesaving support when maximal conventional therapy for cardiorespiratory support is inadequate to maintain oxygenation and perfusion.² Survival after ECMO depends on indication, technique, and timing.³⁻⁵ Furthermore, although ECMO is now accepted for severe, immediate postoperative graft failure, extending its use to other indications is controversial. Therefore, to guide future use, we evaluated our experience with post-lung transplant ECMO, which includes extended indications, to (1) determine its prevalence, risk factors, indications, and timing, (2) compare complications and

Abbreviations and Acronyms

ECMO	= extracorporeal membrane oxygenation
PRA	= panel reactive antibody
VA	= venoarterial
VV	= venovenous

outcomes of these patients with those not requiring it, and (3) identify risk factors, including indications, for mortality.

Patients and Methods

Patients

From February 1990 to October 2005, 474 patients underwent single or double lung transplantation for end-stage lung disease at Cleveland Clinic. Data were extracted from the Unified Transplant Registry, which has been approved for research by the Institutional Review Board of Cleveland Clinic. The Institutional Review Board approved supplemental review of medical records.

ECMO

Support. ECMO was initiated 23 times in 22 patients (4.0%), when oxygenation, ventilation, and tissue perfusion were unable to be supported through conventional methods, including ventilator support with 100% inspired oxygen fraction, pharmacologic paralysis, nitric oxide, high positive end-expiratory pressure, and vasopressors. Median arterial oxygen tension/inspired oxygen fraction was 59 at institution of ECMO (15th and 85th percentiles, 44 and 81), which improved to 164 after ECMO was initiated (15th and 85th percentiles, 81 and 443). Cannulation was peripheral in 20 cases (87%), central in 2 (9%), and combined in 1 (4%). ECMO technique was venoarterial (VA) in 12 (52%) and venovenous (VV) in 11 (48%), based on surgeon preference. As a general rule, VA ECMO was used to support patients with hemodynamic collapse in addition to respiratory failure, and VV ECMO was used for all other patients, without regard to pulmonary artery pressures. Median pulmonary artery systolic pressure was 49 mm Hg at institution of ECMO (15th and 85th percentiles, 27 and 66 mm Hg), which improved to 37 mm Hg after ECMO was initiated (15th and 85th percentiles, 25 and 49 mm Hg).

Circuit. The ECMO circuit has been described previously.⁶ In brief, peripheral or central access was established via wire-reinforced thin-walled polyurethane cannulas (Edwards LifeSciences, Irvine, Calif). The circuit was driven by a centrifugal pump (BP80, Medtronic-BioMedicus, Eden Prairie, Minn) through heparin-coated tubing (Carmeda, Medtronic) and either a hollow-fiber oxygenator (AFFINITY NT, Medtronic) or Maxima-Plus PRF oxygenator (Medtronic) before its discontinuation. All components were heparin coated. Four peripheral cannulas were placed percutaneously, with the remainder being placed by cutdown. Sizes ranged from 16F to 24F. Distal arterial cannulation was used in 2 patients.

Conduct. Systemic heparinization was used with a target activated clotting time of 180 to 250 seconds. Flows were maintained between 2.5 and 3.5 L · min⁻¹. Decision to wean from ECMO was based on radiographic improvement, improved oxygenation, increased graft compliance, and improved hemodynamics.

Risk Factors for Severe Graft Failure Leading to ECMO

Multivariable logistic regression was used for identifying donor and recipient variables (Appendix) associated with ECMO. The process began with initial screening to ensure that at least 5 ECMO events were associated with each dichotomous variable.

Bootstrap aggregation (bagging) was used for variable selection.^{7,8} In brief, automated stepwise variable selection with *P* for inclusion of .1 was performed on 1000 bootstrap samples, and the results were aggregated both by individual factors and by clusters of related factors (such as candidate transformations of scale of continuous and ordered variables). Those appearing in 50% or more of the analyses (median rule) were considered reliably statistically significant at *P* ≤ .1.

Etiology of Graft Failure Necessitating ECMO

Chart review, review of cultures, biopsy tissues, and clinical impressions of the lung transplant team at time of instituting ECMO were used to categorize etiology of graft failure as follows: (1) *early graft failure*, if failure occurred within the first 48 hours of transplant and was due to either an implantation response or a technical problem that was identified and corrected; (2) *acute rejection*, if there was a clinical impression of rejection driving graft failure, usually documented by trans-bronchial biopsies; or (3) *pneumonia or sepsis*, if the clinical impression of the transplant team was infection driving graft failure, with the criteria being purulent bronchoscopy, positive cultures, fever, and leukocytosis.

Timing and Duration of ECMO

Timing of ECMO was calculated as interval from date of operation to date of instituting ECMO. Duration of ECMO was calculated as interval from date of instituting ECMO until its removal or death on ECMO.

Outcomes

Primary outcome was all-cause mortality. Vital status was obtained by cross-sectional follow-up. Mean follow-up duration was 0.73 ± 1.2 years, with 5 of 22 patients (23%) followed for more than 1 year. A total of 16.7 patient-years of data was available for analysis. Survival estimates after ECMO were obtained by the Kaplan-Meier method and a parametric multiphase survival model.⁹ Secondary outcomes were in-hospital complications of ECMO.

Predictors of Mortality

Eight variables were used to identify predictors of mortality after ECMO: (1) date of transplant, (2) single versus double lung transplant, (3-5) etiology of severe graft failure (early graft failure, acute rejection, pneumonia, or sepsis), (6) timing of ECMO, (7) VA versus VV cannulation, and (8) duration of ECMO. Variable selection was as previously described.

Results

Risk Factors for Severe Graft Failure Leading to ECMO

We were unable to identify reliably either recipient or donor demographic, pretransplant clinical, or transplant variables

TABLE 1. Recipient, donor, and transplant characteristics for ECMO and no-ECMO groups

Characteristic	ECMO						P
	Yes (n = 22)			No (n = 452)			
	n*	No.	%	n*	No.	%	
Recipient							
Demography							
Age (y), mean ± SD	22	45 ± 11		452	47 ± 13		.17
Female	22	15	68	452	224	50	.09
Race							
Caucasian	22	21	95	448	410	92	.5
Other	22	1	4.5	448	38	8	.5
Height (cm), mean ± SD	19	166 ± 12		425	167 ± 11		.4
Weight (kg), mean ± SD	21	65 ± 21		444	68 ± 17		.3
BSA (m²), mean ± SD	18	1.7 ± 0.3		418	1.8 ± 0.3		.3
BMI (kg · m⁻²), mean ± SD	18	24 ± 5.5		418	24 ± 5.2		.9
Comorbidity							
Smoking	14	8	57	306	202	66	.5
Hypertension	18	6	33	387	75	19	.15
Underlying disease							
COPD/emphysema	22	7	32	452	171	38	.6
Idiopathic pulmonary fibrosis	22	5	23	452	67	15	.3
Cystic fibrosis	22	4	18	452	78	17	>.9
A1A deficiency	22	2	9.1	452	39	8.6	>.9
Bronchiectasis	22	1	4.6	452	10	2.2	.5
Eisenmenger disease	22	1	4.6	452	6	1.3	.2
Primary pulmonary hypertension	22	1	4.6	452	22	4.9	>.9
Sarcoidosis	22	0	0	452	18	4.0	.3
Immunologic factors							
PRA	21	2.2 ± 4.6		448	1.9 ± 7.7	—	.07
Blood type							
A	21	11	52	443	199	45	.5
O	21	7	33	443	194	44	.3
B	21	3	14	443	50	11	.7
AB	21	0	0	443	0	0	—
Rh factor							
Positive	21	19	90	414	348	84	.4
Negative	21	2	9.5	414	66	16	.4
Donor							
Demography							
Age (y), mean ± SD	19	35 ± 11		426	35 ± 15		.9
Female	21	11	52	446	221	50	.8
Race							
Caucasian	21	19	90	449	391	87	.6
Other	21	2	9.5	449	58	13	.6
Height (cm), mean ± SD	22	167 ± 13		447	169 ± 12		.3
Weight (kg), mean ± SD	21	68 ± 18		446	71 ± 20		.4
BSA (m²), mean ± SD	21	1.8 ± 0.3		446	1.8 ± 0.3		.4
BMI (kg · m⁻²), mean ± SD	21	24 ± 4.9		446	25 ± 5.9		.8
Comorbidity							
Hypertension	18	3	17	381	68	18	.9
Cause of death							
Cerebral bleeding	22	5	23	446	121	27	.6
CNS tumor	22	1	4.6	446	8	1.8	.4
CVA/stroke	22	5	23	446	92	21	.8
Head trauma	22	10	45	446	188	42	.8
Immunologic factors							

TABLE 1. Continued

Characteristic	ECMO						P
	Yes (n = 22)			No (n = 452)			
	n*	No.	%	n*	No.	%	
Blood type							
O	22	12	55	445	264	59	.7
A	22	7	32	445	142	32	>.9
B	22	3	14	445	39	8.8	.4
AB	22	0	0	445	0	0	—
Rh factor							
Positive	20	18	90	439	369	84	.5
Negative	20	2	10	439	70	16	.5
Transplant							
Type of transplant							
Single	22	12	55	450	256	57	.8
Double	22	10	45	450	194	43	.8
Cold ischemic time (min),† mean ± SD	20	302 ± 175		363	280 ± 145		>.9
BMI							
Difference,‡ mean ± SD	17	−0.38 ± 8.2		413	−0.76 ± 7.5		>.9
Ratio,§ mean ± SD	17	1.02 ± 0.29		413	1.01 ± 0.3		.7
BSA							
Difference,‡ mean ± SD	17	−0.03 ± 0.37		413	−0.06 ± 0.33		.6
Ratio,§ mean ± SD	17	1 ± 0.19		413	0.99 ± 0.18		.6
Interval from 1/1/1990 to index	22	9.6 ± 4.7		452	10 ± 4.3		.7
Operation, mean ± SD							

A1A, Alpha-1a antitrypsin; BMI, body mass index; BSA, body surface area; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; ECMO, extracorporeal membrane oxygenation; PRA, panel reactive antibody; SD, standard deviation. *Data available.

†Longest ischemic time if double lung transplant. ‡Recipient–donor. §Recipient/donor.

that predicted severe graft failure leading to ECMO (Table 1). Variables not found to be associated with severe graft failure included cold ischemic time, panel reactive antibody (PRA) level, and donor-to-recipient size match.

Etiology of Graft Failure Necessitating ECMO

The most common indication for ECMO was early graft failure (n = 13, 57%), followed by pneumonia or sepsis (n = 6, 26%) and acute rejection (n = 4, 17%). Three patients with early graft failure had left atrial anastomotic complications that caused pulmonary congestion and necessitated reoperation. Another had important bleeding from dense pleural adhesions that led to high transfusion requirement and multiple reoperations. All others (n = 9) had severe graft failure of unclear etiology that could be termed “primary graft dysfunction”¹⁰; we elected to use the term “early graft failure,” however, because of the unclear etiology yet early temporal relationship to transplantation. Three patients required ECMO for acute rejection, with 1 of the 3 requiring 2 separate ECMO runs. Acute rejection was diagnosed by transbronchial biopsy and treated with plasmapheresis and antithymocyte globulin. No patient underwent acute retransplantation.

Timing and Duration of ECMO

ECMO was initiated at a median of 2 days postoperatively (range, 0–21 days; 15th and 85th percentiles, 0 and 12 days; Figure 1). It was instituted earliest for severe graft failure (generally within 2 days of lung transplant), was instituted over a broad range of timing for pneumonia or sepsis, but generally later than for severe graft failure, and was concentrated within the second week for acute rejection. ECMO was maintained for a median of 4 days (range, 2–17 days; 15th and 85th percentiles, 3 and 10 days; Figure 2). Median duration was longest in the pneumonia/sepsis group (7 days; *P* [Wilcoxon] for differences among groups = .03). VA and VV ECMO were similarly effective in reducing pulmonary artery pressures.

Complications of ECMO

Twenty of 22 patients (90%) had at least 1 complication directly attributable to ECMO (Table 2). The most commonly occurring complications were renal failure necessitating dialysis (57%) and bleeding necessitating reoperation (43%). Complications occurred with both VA and VV ECMO, with similar prevalence (*P* = .5). Complications were associated with both peripheral and central cannulation techniques, although the small number of central cannulations (2) precluded

Figure 1. Relation of indication for ECMO and its timing (interval from lung transplant to institution of ECMO). ECMO, extracorporeal membrane oxygenation.

meaningful comparison. There were no deep vein thromboses in either patient cannulated centrally.

Survival After ECMO

We compared survival after ECMO against survival of all other patients undergoing lung transplantation at Cleveland Clinic between February 1990 and October 2005 (Figure 3, A). Initially, risk of death was substantially higher in the ECMO group, but patients surviving beyond 1 year had a risk of death not importantly different from that of those not placed on ECMO (Figure 3, B).

Figure 2. Duration of ECMO according to etiology. ECMO, extracorporeal membrane oxygenation.

TABLE 2. ECMO complications (n = 23 among 22 patients)

Complication	No.*	% of 23
Renal failure necessitating dialysis	13	57
Bleeding necessitating reoperation	10	43
Deep vein thrombosis	5	22
Cerebrovascular accident	3	13
Lower extremity ischemia	3	13
Common femoral vein injury	2	8.6
Deep vein thrombosis and pulmonary embolus	1	4.3
Heparin-induced thrombocytopenia	1	4.3
Hemoptysis	1	4.3
Lymphocele	1	4.3
Nasopharyngeal bleeding	1	4.3
Compartment syndrome requiring fasciotomy	1	4.3
Atrial fibrillation	1	4.3

*Number of patients experiencing each complication; individual patients could experience more than 1 complication. ECMO, extracorporeal membrane oxygenation.

Predictors of Mortality

Of the 8 variables evaluated, the only 1 associated with worse outcome was instituting ECMO for pneumonia or sepsis (Figure 4). Survival was similar in patients supported for acute rejection and early graft failure.

Discussion

Most transplant centers perform ECMO for severe early graft failure (within 48 hours of transplant), because there is an impression that outcomes are poor for other indicators. Our study focused on patients supported with ECMO beyond the early postoperative period and for extended indications.

Principal Findings

Risk factors for severe graft failure leading to ECMO. We were unable to identify risk factors for severe graft failure leading to ECMO after lung transplantation. This may be because graft failure severe enough to require ECMO was uncommon, with a prevalence of only 4%. We were not able to reproduce results of others showing that recipient diagnosis of primary pulmonary hypertension, mismatch of donor and recipient size, or female gender were predictive of need for ECMO.^{4,11,12} Although PRA levels have been shown to be predictive of survival after lung transplantation,¹³ they were not predictive of need for ECMO.

Etiology of graft failure necessitating ECMO. As in other studies, early graft failure was the most common indication for ECMO in our patients, followed by pneumonia or sepsis. We agree with the movement to standardize the term “primary graft dysfunction” to define lung injury occurring after graft implantation¹⁰ and are incorporating this term prospectively. However, in this study, we used the term “early graft failure” because of our difficulty differentiating the role of transfusion requirement and pulmonary venous complications leading to ECMO in 3 patients.

Figure 3. Death after ECMO (open circles) and death in all others after lung transplant (closed circles). **A**, Survival. Each circle represents a death, vertical bars are asymmetric 68% confidence intervals for these estimates (equivalent to ± 1 standard error), and numbers in parentheses represent patients alive at various time points. Solid lines represent parametric estimates enclosed within 68% confidence limits. **B**, Hazard function (instantaneous risk of death), ECMO, extracorporeal membrane oxygenation.

Timing and duration of ECMO. Our median timing overall of initiating ECMO, postoperative day 2, was slightly later than recently reported series in which ECMO was almost universally initiated within the first 2 days of transplant.^{12,14} However, this relates at least in part to our extended use of ECMO that, in comparison, resulted in instituting ECMO over a wide range of postoperative days, with the latest being day 21. We have confirmed that patients can still be salvaged when placed on ECMO later in their hospital course, particularly those experiencing acute rejection, although numbers are small.¹⁵ In addition, we have shown that survival is possible in patients who require longer periods of ECMO support, with 1 patient being discharged alive from the hospital after 17 days on ECMO.

Complications of ECMO. Nearly all our patients had complications directly attributable to ECMO. Complica-

Figure 4. Survival after ECMO according to indication for ECMO. Format is similar to that of Figure 3, **A**, except closed circles represent ECMO for early graft failure and acute rejection, and open circles represent ECMO for pneumonia or sepsis, ECMO, extracorporeal membrane oxygenation.

tions seem inherent in the ECMO circuit, primarily because it requires large cannulas that are thrombogenic despite their heparin coating and that can lead to distal limb malperfusion and thromboembolism. In addition, need for anticoagulation to prevent or treat thromboembolism, as well as hemolysis resulting from the ECMO circuit, predispose patients with fresh operative fields to bleeding. Bleeding complications were not directly related to level of anticoagulation and occurred in the face of normal thrombocyte counts.

We have become increasingly aggressive about diagnosing and treating deep vein thrombosis and use inferior caval filters after decannulation when proximal deep vein thrombosis has been identified. Dialysis requirement reflects multifactorial injury to the kidneys that occurs secondarily to hemodynamic instability, vasopressor use, sepsis, direct effects of the ECMO circuit, and effects of multiple nephrotoxic drugs. Although multiple antibiotics were used to treat sepsis, we did not alter our routine postoperative antifungal therapy as prophylaxis for patients on ECMO.

Survival after ECMO. Survival after ECMO was reasonable and consistent with that of other reports, with salvage possible in a group of patients who would otherwise have died. Survival was best in patients treated for early graft failure and acute rejection. Interestingly, hazard curves for patients needing ECMO versus those who did not became equivalent at 1 year, suggesting that initial factors leading to ECMO and the ensuing difficult postoperative course can be overcome without affecting long-term survival.

Predictors of mortality. Of the 8 variables evaluated as predictors of mortality for patients requiring ECMO (Figure 3), we were able to identify only 1: institution of ECMO for sepsis or pneumonia. Other studies have suggested that VV was preferable to VA ECMO,¹² that the era in which ECMO was

instituted was a risk factor,³ and that instituting ECMO late (>7 days) after transplant was almost never successful.⁵ A multivariable analysis did not identify any of these factors as predictors of mortality, although this may be due to small numbers and confounding of multiple variables (for example, timing of ECMO and etiology of graft failure leading to ECMO). Our study does support Meyers and colleagues'⁴ finding that outcomes were poor after ECMO use in infected patients. Although our study showed similar outcomes of VA and VV ECMO, we have gravitated toward use of VV even in the setting of pulmonary hypertension and hemodynamic compromise. Correction of acidosis, carbon dioxide clearance, and improved oxygenation provided by the VV circuit rapidly lower pulmonary artery pressures and improve systemic hemodynamics. We reserve VA ECMO for patients with high vasopressor requirements and imminent circulatory arrest.

Limitations

The primary limitation of this study is that it represents clinical experience at a single center with low prevalence of severe graft failure leading to ECMO. In addition, diagnosing early graft failure, acute rejection, and pneumonia or sepsis can be difficult, and etiology may be multifactorial. Biopsy in the setting of severe hypoxia or anticoagulation is frequently not possible, and positive cultures can represent colonization as well as active infection. In addition, the criteria for VA versus VV ECMO were not well defined and were influenced by multiple factors, including hemodynamics, surgeon preference, and era of transplantation.

Conclusions

Our study has shown that ECMO can be used with reasonable results to salvage patients with severe graft failure after lung transplantation. We have learned to consider carefully all patients with severe graft failure for ECMO and to extend its use selectively past the initial perioperative period, particularly to those with acute rejection.

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Appendix: Variables Used in Analyses

Recipient

Demographic: Gender, age (years), height (cm), weight (kg), body surface area (m²), body mass index (kg · m⁻²)

Diagnosis: Chronic obstructive pulmonary disease, emphysema, cystic fibrosis, idiopathic pulmonary fibrosis, hypertension

Immunology: Blood type, PRA level (%)

Transplant: Single, double; ischemic time (min); interval from January 1, 1990 to index surgery

Donor

Demographic: Gender, age (years), height (cm), weight (kg), body surface area (m²), body mass index (kg · m⁻²)

Immunology: Blood type

Cause of death: Cerebral bleeding, cardiovascular accident, head trauma

Comorbidity: Hypertension

Donor-Recipient

Demographic: Difference in body mass index (recipient – donor), body mass index ratio (recipient/donor), difference in body surface area (recipient – donor), body surface area ratio (recipient/donor)

ECMO: VV versus VA cannulation