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Spontaneously Breathing Extracorporeal Membrane Oxygenation Support Provides the Optimal Bridge to Lung Transplantation

Matthew Adam Schechter, MD¹, Asvin M. Ganapathi, MD¹, Brian R. Englum, MD¹, Paul J. Speicher, MD¹, Mani A. Daneshmand, MD¹, R. Duane Davis, MD¹, and Matthew G. Hartwig, MD¹

¹ Department of Surgery, Duke University Medical Center, Durham, NC

Abstract

Background—Extracorporeal membrane oxygenation (ECMO) is being increasingly used as a bridge to lung transplantation. Small, single-institution series have described increased success using ECMO in spontaneously breathing patients compared with patients on ECMO with mechanical ventilation, but this strategy has not been evaluated on a large scale.

Methods—Using the United Network for Organ Sharing database, all adult patients undergoing isolated lung transplantation from May 2005 through September 2013 were identified. Patients were categorized by their type of pretransplant support: no support, ECMO only, invasive mechanical ventilation (iMV) only, and ECMO + iMV. Kaplan-Meier survival analysis with log-rank testing was performed to compare survival based on type of preoperative support. A Cox regression model was used to determine whether type of preoperative support was independently associated with survival, using previously established predictors of survival as covariates.

Results—Approximately 12,403 primary adult pulmonary transplantations were included in this analysis. Sixty-five patients (0.52%) were on ECMO only, 612 (4.93%) required only iMV, 119 (0.96%) were on ECMO + iMV, and the remaining 11,607 (94.6%) required no invasive support before transplantation. One-year survival was decreased in all patients requiring support, regardless of type. However, mid-term survival was similar between patients on ECMO alone and those not on support but significantly worse with patients requiring iMV only or ECMO + iMV. In multivariable analysis, ECMO + iMV and iMV alone were independently associated with decreased survival compared with nonsupport patients, whereas ECMO alone was not significant.

Conclusions—In patients with worsening pulmonary disease awaiting lung transplantation, those supported via ECMO with spontaneous breathing demonstrated improved survival compared with other bridging strategies.

Correspondence: Matthew G. Hartwig, MD, Division of Thoracic Surgery, Duke University Medical Center, Box 3863, Durham, NC 27710. (matthew.hartwig@dm.duke.edu).

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For certain patients with advanced lung diseases, lung transplantation is the only therapeutic option.¹ Unfortunately, given the scarcity of donor organs, patients on the waiting list may progress to respiratory failure, requiring invasive respiratory support until a suitable organ becomes available. For many patients, initial support consists of invasive mechanical ventilation (iMV), and if their clinical situation deteriorates further, or iMV is unreasonable, patients are placed on extracorporeal membrane oxygenation (ECMO). However, as ECMO technology has improved, bridging strategies have evolved such that iMV and ECMO may be used separately or in combination. Previous research indicates both of these support mechanisms are associated with worse outcomes after lung transplantation,²⁻⁷ in part because of the severity of the underlying disease and also because of the morbidity associated with mechanical support. On the contrary, some single centers' bridging experiences with "awake" ECMO suggest similar early survival to nonbridged recipients is possible.^{8,9} These bridging strategies are being increasingly used before lung transplantation,¹⁰ and thus, determining the optimal use of them is of utmost importance.

An emerging concept for bridging support is ECMO in nonintubated patients.^{8,11-20} In addition to demonstrating the feasibility of this bridge strategy, these reports also suggest that by allowing the patient to remain extubated—and in some cases, ambulatory—not only are the risks of prolonged intubated avoided but nutritional and functional status can be better optimized before transplantation. Nevertheless, the literature on this topic remains limited to case reports and small, single center series, limiting the ability to determine whether this strategy could affect posttransplantation outcomes. Therefore, the aim of this study was to evaluate the effect of nonintubated ECMO on survival after lung transplantation using a national registry.

MATERIALS AND METHODS

The study protocol was approved by the Duke University institutional review board and met exempt status.

Study Design and Patient Selection

The United Network for Organ Sharing (UNOS) national database was queried for all US adult lung transplantations recorded between May 2005 and September 2013. Patients who underwent repeat or multiorgan transplant or were younger than 18 years at transplantation were excluded. The remaining patients were categorized by level of respiratory support at the time of transplantation: iMVonly, ECMO only, ECMO + iMV, and no invasive respiratory support. The specific type of ECMO (ie, venovenous, venoarterial) is not specified in the database and, therefore, could not be included in the analysis. The primary study outcome was survival. Secondary outcomes available in UNOS of clinical relevance included new-onset dialysis, an episode of acute rejection before discharge and length of posttransplant hospitalization stay. To determine whether there was escalation or de-escalation of the patient's care during the bridging period, the level of respiratory support at the time of listing was compared between the different bridging strategies. Infection requiring IV antibiotics within 2 weeks of transplantation and patients receiving a blood transfusion between listing and transplantation were used in an attempt to determine

differences in infection and bleeding complications, respectively, between the different bridging strategies.

The UNOS database for was also queried for all patients listed for initial lung transplantation during the same period, and the reason for removal from the list (ie, transplanted, death, condition either deteriorated or improved) was compared by level of respiratory support at the time of listing.

Statistical Analysis

After identification and stratification of patients meeting study criteria, unadjusted descriptive comparisons of donor, recipient, and procedural characteristics were done between the different bridging strategies using the chi-square test and ANOVA for categorical and continuous variables, respectively. Kaplan-Meier analysis with the log-rank test estimated differences in long-term survival between the different bridging strategies and each bridge strategy compared with patients not requiring support. To test whether the type of preoperative respiratory support was an independent risk factor for survival, a Cox regression model was created incorporating characteristics known to influence outcomes. These characteristics included patient age, indication for transplantation, total serum bilirubin, serum creatinine, forced vital capacity (FVC, %), forced expiratory volume in 1 second (FEV1, %), donor age, and diabetic donor. Specific listing diagnoses were categorized into the 4 groups used to determine the lung allocation score (Table 1²¹). Length of stay was compared among the 3 bridge strategies using ANOVA. The incidence of acute rejection before discharge and new-onset dialysis was compared using the chi-square test.

Categorical variables were presented as frequencies and percentages, whereas continuous variables were expressed as mean $\pm$ standard deviation (SD) or median with interquartile range (IQR). A $P < 0.05$ was considered significant. All analyses were conducted with Stata version 12.1 (StataCorp, College Station, TX).

RESULTS

During the study period, a total of 12,403 adult patients underwent initial lung transplantation. Of these, 796 (6.4%) required some form of invasive respiratory support before transplantation, with 65 (0.52%) on ECMO only, 612 (4.9%) on iMV only, and 119 (0.96%) patients on both ECMO and iMV. Table 2 outlines the recipient, donor, and procedural characteristics of the patient groups. Among the different bridge strategies, there were significant differences in the age of the recipient, indications for transplantation, pretransplant FEV1, mean pulmonary artery pressure, total bilirubin, type of respiratory support before transplant, dialysis before transplant, lung allocation score, and ischemic time. A significantly higher percentage of patients who had ECMO as part of their bridging strategy, with or without iMV, received blood transfusions before transplantation compared with those only on iMV (ECMO only: 40.0%, ECMO + iMV: 38.7%, iMV only: 16.5%; $P < 0.0001$). There was no difference in the rate of infection requiring IV antibiotics between the 3 groups ($P = 0.38$). Of the 65 patients on ECMO only at time of transplant, 11 (16.9%) had been on a different form of respiratory support at time of listing, compared with only 3 (0.5%) in the iMV only group. Within the ECMO + iMV group, 27 (22.6%) had been on

only a single type of respiratory support at the time of listing. There were no differences in donor characteristics between the groups.

Kaplan-Meier analysis with the log-rank test identified a significant difference in long-term survival between the 3 different bridge strategies ($P = 0.0097$; Figure 1). Cumulative survival for ECMO-only patients at 6 months, 1 year, and 3 years was 75.2%, 70.4%, and 64.5%, compared with 79.9%, 72.0%, and 57.0% for mechanically ventilated patients and 68.1%, 61.0%, and 45.1% for patients requiring both iMV and ECMO. For patients who required no support before transplantation, survival at 6 months, 1 year, and 3 years was 89.4%, 84.2%, and 67.0%. Although patients on ECMO alone had a worse 1-year survival compared with unsupported recipients (70.4% vs. 84.2%, respectively), mid-term survival for patients on ECMO alone was not significantly different ($P = 0.16$). However, patients requiring either iMV alone or ECMO + iMV had significantly worse survival compared with patients not requiring support ($P < 0.0001$ for both). After adjustment with a multivariate Cox regression model, iMV +/- ECMO was independently associated with worse survival compared with patients not requiring mechanical bridge (iMV only: hazard ratio [HR] = 1.46; iMV + ECMO = 2.26, $P < 0.0001$ for both), whereas ECMO alone was not ($P = 0.39$; Table 3).

With regard to the perioperative outcomes (Table 4), the incidence of new-onset dialysis was significantly different among the bridging strategies ($P < 0.0001$), with ECMO + iMV patients having the highest incidence (23.5%) compared with both ECMO only patients (13.9%) and iMV only (10.3%). ECMO-only patients had a shorter length of stay (median, 25; IQR, 19-39.5) than either iMV alone (median, 27; IQR, 18-46) or ECMO + iMV (median, 32; IQR, 19-58), although this difference did not reach statistical significance ($P = 0.076$). The incidence of rejection before discharge was also the lowest among the ECMO only patients (10.8% vs. 12.9% [iMV only] vs. 18.5% [ECMO + iMV]), but again, this difference did not reach statistical significance ($P = 0.21$).

Of the 20,714 patients listed for transplantation, 528 (2.5%) had invasive mechanical support at the time of listing. Thirty-two patients (0.15%) were on ECMO alone at time of listing, 431 (2.1%) were on iMV only, and 62 (0.3%) were on ECMO + iMV. Of the 32 patients on ECMO at time of listing, 22 (68.8%) were transplanted, whereas 6 (18.8%) either died or their condition deteriorated such that they were removed from the list. For the patients listed on iMV alone, 231 (53.4%) were transplanted, with 109 (41.4%) either dying or becoming too sick for consideration. For the patients listed on ECMO and iMV, 38 (61.2%) were transplanted, whereas 21 (33.9%) either died or deteriorated. These differences in outcomes after listing were statistically significant ($P = 0.004$).

DISCUSSION

Previous studies have shown that pretransplant ECMO is associated with worse survival after lung transplantation compared with unsupported patients.^{3,5,6,10} However, these papers did not separate those on only ECMO from those on both ECMO and iMV, most likely because of the rarity of nonintubated ECMO patient. Analysis of a large, national database showed that less than 0.5% of primary lung transplants within the last decade were bridged using ECMO alone. This current analysis found that the long-term survival of patients

supported by ECMO alone was not significantly different compared with unsupported patients requiring no invasive bridge. However, in both univariable and multivariable analysis, mechanical ventilation—with or without ECMO support—was associated with significantly decreased survival. These results suggest that in selected patients, ECMO without mechanical ventilation affords a survival benefit compared with the other bridging strategies for lung transplantation.

Initial use of ECMO as a bridge to lung transplantation was associated with high mortality and major morbidity, so was largely abandoned.²² Advances in technology and more experience with ECMO helped improve outcomes, but it was still considered a heroic bridging technique for patients' refractory to maximal ventilator support. However, an increasing body of literature primarily consisting of individual cases or small series of patients has highlighted the concept of using ECMO in lieu of mechanical ventilation as the primary bridging support device.^{8,13-20} The largest of these series, by Fuehner and colleagues, describes 20 patients successfully bridged to transplantation using awake ECMO and reports a 6-month survival equal to this study (16/20, 80%).⁸ Although they compare outcomes with a historical cohort of mechanically ventilated patients, the majority of this control group required extracorporeal support in addition to mechanical ventilation, confounding any findings. Through the use of a national registry, this study not only provides a largest group of nonintubated ECMO patients but also has robust enough numbers to examine iMV only and ECMO + iMV separately.

There are some underlying differences demographic differences among the groups presented here. For example, patients receiving ECMO, with or without iMV, tended to be younger than patients only on iMV and unsupported patients. This finding is consistent with previous studies^{3,6,10,17} and likely reflects the use of a lower age threshold for pretransplant ECMO than for standard lung transplantation, given the concerns over the morbidity of this bridge strategy. At the same time, patients on ECMO had more evidence of multiple organ system dysfunction, as evidenced by a higher incidence of dialysis, lower GFR, and elevated bilirubin before transplantation. The overall acuity of these patients helps explain the decreased 1-year survival among the ECMO-only patients. However, finding that the overall survival of the ECMO-only patients is comparable to patients transplanted without support, despite a more critical clinical presentation, speaks to the overall effectiveness of this bridging strategy.

One advantage of using only ECMO as a bridging strategy is the avoidance of the risks that come with mechanical ventilation. Studies have shown that even short periods of mechanical ventilation can cause general muscle atrophy, and this wasting occurs to a greater extent in the diaphragm than in the peripheral muscles.²³⁻²⁵ Mechanical ventilation causes structural abnormalities of the subcellular components of diaphragmatic fibers and maladaptive fiber remodeling, decreasing the overall endurance of the diaphragm.^{23,26} This atrophy and structural injury can lead to difficult and prolonged weaning after lung transplantation, which would not only increase the risk of complications but also prolong ICU and overall hospitalization stays. In this study, both the iMV only and ECMO and iMV groups had longer posttransplant hospitalization stays compared with the ECMO-only group, which could be in part due to ventilator-induced deconditioning. iMV may also trigger pulmonary

and systemic inflammatory responses,^{27,28} and increased exposure to chemokines and other inflammatory mediators has been shown to affect both acute rejection²⁹ and long-term graft survival.³⁰

Extracorporeal membrane oxygenation without mechanical ventilation also affords the opportunity to actively rehabilitate the patient. Several reports have discussed the ability of nonintubated ECMO patients to participate in physical therapy and improve their nutritional status before transplantation.^{8,9,15,31} The potential to not only bridge patients to lung transplant, but bridge and optimize them using awake ECMO, may help to explain the improved outcomes seen in this current study. Avoiding the sedation required for oral intubation or the extreme support required for many of these end-stage lungs allows for an active exercise routine to be carried out on ECMO. This in turn has led to decreased posttransplant myopathy complications.⁹

Extracorporeal membrane oxygenation is not without its own complications, including bleeding, thrombosis, infection, renal failure, and neurologic changes,³² which may affect the overall effectiveness of ECMO as a bridging strategy. In this study, patients bridged to transplant using ECMO, with or without iMV, were more likely to have received a transfusion compared with only mechanically ventilated patients, suggesting there was an increased frequency of bleeding with these patients. This finding is further corroborated by the fact that the percentage of ECMO patients who received a pretransplant transfusion is similar to the reported incidence of bleeding complications in other studies on ECMO.^{32,33} As the need for pretransplant intravenous antibiotic therapy was not significantly different between the bridging strategies, there does not seem to be increased infectious complications with ECMO during the bridging period. Whether the increased percentage of the ECMO-bridged patients on dialysis before transplant is a result of the ECMO itself or their overall disease state is difficult to ascertain. Although this database does not include patients deemed too sick for even listing, the fact that most patients on ECMO at listing were transplanted suggests that the potential complications of ECMO did not seem to interfere with their ability to undergo transplantation,

Although this is the largest series examining spontaneously breathing ECMO as a bridge to lung transplantation, there are limitations to acknowledge. First, as this is a national registry, there are relevant recipient factors that are not captured, particularly in regard to the ECMO therapy. The type of cannulation technique, equipment used, ambulation status of the patient, and length of ECMO support are not known, but such variables likely affect posttransplant survival. Important outcomes, such as complications directly resulting from these bridge strategies, operative time, length of posttransplant mechanical ventilation, and ICU stay, are also not recorded. Another limitation is that this study focuses on only those patients who were listed for transplantation, introducing potential selection bias. Finally, the retrospective nature of this study has the potential to introduce unexpected biases as well.

In conclusion, within a large national database, patients bridged to lung transplant with ECMO alone have a long-term survival comparable to those not requiring support, in contrast to the other bridging strategies using mechanical ventilation. Further research is needed to determine the optimal patients and optimal parameters for nonintubated ECMO

support, and a more thorough comparison between the bridging strategies (ie, a multicenter randomized control trial) is also required. However, these findings argue for determining how to best use this bridging strategy in a rapidly deteriorating patient awaiting lung transplantation.

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FIGURE 1.
Kaplan-Meier survival curve, by pretransplant support.

TABLE 1

Diagnostic categories and component diagnoses used in calculating the Lung Allocation Score. Adapted from Egen et al²¹

Group A	Group B	Group C	Group D
Chronic obstructive pulmonary disease	Primary pulmonary hypertension	Cystic fibrosis; immune deficiency syndromes, for example, IgG deficiency	Idiopathic pulmonary fibrosis
Emphysema	Eisenmenger syndrome		All other restrictive lung diseases, including hemosiderosis
Alpha-one antitrypsin deficiency emphysema	All specific pulmonary vascular diseases, including pulmonary venous obstructive disease, chronic pulmonary thromboembolic disease		Eosinophilic granulomatosis
Bronchiectasis, including primary ciliary dyskinesia			Sarcoidosis with mean PA pressure >30 mmHg
Lymphangioleiomyomatosis			Scleroderma/CREST
Sarcoidosis without mean PA pressure >30 mmHg			Bronchoalveolar carcinoma

TABLE 2

Recipient, donor, and procedural characteristics

	No support (n = 11607)	ECMO only (n = 65)	iMV only (n = 612)	ECMO + iMV (n = 119)	P (Bridging strategies)
Recipient					
Age	55.2 ± 12.7	47.6 ± 14.6	51.9 ± 15.2	47.8 ± 15.5	0.004
BMI	25.1 ± 4.6	24.6 ± 5.1	24.8 ± 5.3	24.4 ± 5.1	0.76
Sex (male)	6917 (59.6%)	44 (67.7%)	350 (57.2%)	70 (58.8%)	0.262
Indication for transplant, by diagnostic category					<0.0001
Group A (obstructive)	4013 (34.6%)	5 (7.7%)	145 (23.7%)	8 (6.7%)	
Group B (vascular)	365 (3.1%)	7 (10.8%)	17 (2.8%)	4 (3.4%)	
Group C (cystic fibrosis)	1365 (11.8%)	10 (15.4%)	119 (19.4%)	27 (22.7%)	
Group D (restrictive)	5864 (50.5%)	43 (66.2%)	331 (54.1%)	80 (67.2%)	
Level of respiratory support at listing					<0.0001
No support	11556 (99.6%)	47 (72.3%)	446 (72.9%)	63 (52.9%)	
ECMO only	4 (0.03%)	7 (10.8%)	1 (0.2%)	10 (8.4%)	
iMV only	45 (0.39%)	6 (9.2%)	163 (26.6%)	17 (14.3%)	
ECMO + iMV	2 (0.02%)	5 (7.7%)	2 (0.3%)	29 (24.4%)	
FEV1 (% predicted)	38.5 ± 21.0	44.6 ± 22.7	38.8 ± 20.8	43.4 ± 22.0	0.038
FVC (% predicted)	49.2 ± 17.7	48.4 ± 19.2	46.4 ± 18.2	44.9 ± 20.1	0.54
Cardiac output (L/min)	5.3 ± 1.4	5.5 ± 1.6	5.5 ± 1.5	5.5 ± 2	0.89
Mean pulmonary artery pressure (mmHg)	27.1 ± 10.6	35.1 ± 14	29.5 ± 11.1	29.7 ± 11.6	0.003
Creatinine	0.9 ± 0.4	0.9 ± 0.7	0.8 ± 0.5	0.8 ± 0.5	0.20
Glomerular filtration rate	87.5 (72.9, 110.0)	97.3 (66.8, 135.8)	99.4 (74.3, 139.5)	105.6 (74.0, 151.6)	0.11
Total bilirubin	0.5 (0.3, 0.7)	0.8 (0.5, 1.4)	0.5 (0.3, 0.7)	0.8 (0.5, 1.2)	<0.0001
Dialysis Before Transplant	37/10358 (0.36%)	6/48 (12.5%)	10/412 (2.4%)	10/92 (10.1%)	<0.0001
Transfusion between listing and transplantation	336 (2.9%)	26 (40.0%)	101 (16.5%)	46 (39.7%)	<0.0001
Infection requiring IV antibiotics	945 (8.2%)	25 (38.5%)	208 (34.0%)	50 (42.0%)	0.38
Lung allocation score	38.9 (34.3, 47.5)	90.7 (75.7, 92.6)	67.4 (40.9, 89.4)	90.4 (83.3, 92.8)	<0.0001
Days on waitlist	73 (22, 226)	21 (7, 74)	28 (7, 111)	12 (6, 61)	0.11
Donor					
Age	33.6 ± 14.1	34.8 ± 13.5	34.9 ± 14.3	34.0 ± 15	0.70
BMI	25.4 ± 5.1	26.0 ± 4.0	25.6 ± 5.3	25.5 ± 5.6	0.93
Sex (male)	7031 (60.6%)	35 (53.8%)	332 (54.2%)	69 (58.0%)	0.75
Diabetes	777 (6.7%)	2 (3.1%)	50 (8.2%)	5 (4.2%)	0.28
History of cigarette use	122 (11.4%)	7 (10.8%)	80 (13.1%)	10 (8.4%)	0.34
Type of transplant					0.32
Single	4141 (35.7%)	7 (10.8%)	106 (17.3%)	17 (14.3%)	
Double	7466 (64.3%)	58 (89.2%)	506 (82.7%)	102 (85.7%)	
CMV Mismatch	3000 (26.1%)	24 (36.9%)	119 (32.7%)	37 (31.1%)	0.72

	No support (n = 11607)	ECMO only (n = 65)	iMV only (n = 612)	ECMO + iMV (n = 119)	P (Bridging strategies)
Ischemic time (hr)	5.1 ± 1.7	5.9 ± 1.5	5.5 ± 1.7	6.0 ± 1.9	0.027

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TABLE 3

Factors affecting mortality after primary lung transplantation from May 2005 to September 2013, multivariate analysis (n = 12 403)

	Hazard ratio	95% Confidence interval	P
Recipient age (per year)	1.010	1.007-1.015	<0.0001
Indication for transplant, by diagnostic category			
Group A (obstructive)	1 (reference)		
Group B (vascular)	1.372	1.14-1.65	0.001
Group C (cystic fibrosis)	1.193	1.04-1.37	0.013
Group D (restrictive)	1.102	0.99-1.21	0.052
Total bilirubin	1.034	1.01-1.06	0.003
Creatinine	1.114	1.06-1.17	<0.0001
FVC (%)	0.996	0.993-0.998	0.001
FEV1 (%)	1.001	0.998-1.004	0.44
Preoperative support			
No support	1 (reference)		
ECMO only	1.263	0.75-2.14	0.39
Vent only	1.460	1.28-1.66	<0.0001
ECMO + iMV	2.257	1.59-3.20	<0.0001
Donor age (per year)	1.002	1.000-1.004	0.089
Diabetic donor	1.093	1.03-1.16	0.004

TABLE 4

Postoperative outcomes, by level of preoperative support

	No support (n = 11607)	ECMO only (n = 65)	iMV only (n = 612)	ECMO + iMV (n = 119)	P (bridging strategies)
Length of stay	15 (10, 24)	25 (19, 39.5)	27 (18, 46)	32 (19, 58)	0.076
Acute rejection before discharge	997 (8.7%)	7 (10.8%)	79 (12.9%)	22 (18.5%)	0.21
Need for dialysis	552 (4.8%)	9 (13.9%)	63 (10.3%)	28 (23.5%)	<0.0001