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Active rehabilitation during ECMO as a bridge to lung transplantation

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Abstract

Background: Patients with end-stage lung disease often progress to critical illness, which dramatically reduces their chance of survival following lung transplantation. Pre-transplant deconditioning has a significant impact on outcomes for all lung transplant patients and is likely a major contributor to increased mortality in critically ill lung transplant recipients. The aim of this report is to describe a series of patients bridged to lung transplant with extracorporeal membrane oxygenation (ECMO) and examine the potential impact of active rehabilitation and ambulation during pre-transplant ECMO.

Methods: This retrospective case series reviews all patients bridged to lung transplantation with ECMO at a single tertiary care lung transplant center. Pre-transplant ECMO patients receiving active rehabilitation and ambulation were compared to those patients who were bridged with ECMO but did not receive pre-transplant rehabilitation.

Results: Nine consecutive patients between April 2007 and May 2012 were identified for inclusion. One year survival for all patients was 100%, with one patient alive at 4 months post-transplant. The five patients participating in pre-transplant rehabilitation had shorter mean post-transplant length of mechanical ventilation (4 days vs. 34 days, $p = 0.01$), ICU stay (11 days vs. 45 days, $p = 0.01$), and hospital stay (26 days vs. 80 days, $p = 0.01$). No patients who participated in active rehabilitation had post-transplant myopathy, compared to three of four patients who did not participate in pre-transplant rehabilitation on ECMO.

Conclusions: Bridging selected critically ill patients to transplant with ECMO is a viable treatment option, and active participation in physical therapy, including ambulation, may provide a more rapid post-transplantation recovery. This innovative strategy requires further study to fully evaluate potential benefits and risks.

Introduction

Over the past ten years, the number of lung transplants performed on an annual basis has consistently risen, with over 3200 patients transplanted in 2009 at over 125 international centers [1]. Pre-transplant conditioning is an important predictor of morbidity and mortality in these patients [2,3], and almost all centers require lung transplant candidates to participate in pulmonary rehabilitation prior to transplant. Patients must have a degree of illness that warrants listing and lung transplantation; however, deteriorating clinical status prior to transplantation may significantly decrease the likelihood of transplant success and survival [1,4,5].

The subset of patients who become critically ill and require mechanical ventilation (MV) prior to lung transplantation have significantly lower survival, with a decrease in overall one year survival rate from 80% to 63.7% [1]. The relative risk of death in patients requiring life support pre-transplantation is 1.57 (95% Confidence Interval, 1.31 – 1.88) in the year following transplant when compared to those patients who do not require pre-operative life support [1]. Mortality is even higher in critically ill patients who continue to deteriorate and require extracorporeal membrane oxygenation (ECMO) prior to transplantation [5-8]. As reported outcomes in patients supported pre-transplantation with ECMO are poor, the use of ECMO as a bridge to lung transplantation has been quite limited [1,4,8-11].

Mortality in transplant patients supported with ECMO is often related to the degree of organ dysfunction, but an important additional contributor is pre-transplant deconditioning [2,3]. This deconditioning, while commonplace in critically ill patients, is often further exacerbated in those patients who require ECMO secondary to cannulation techniques, immobility, and sedation practices [12]. Recently published data by Fuehner, et. al. demonstrate improved survival in patients bridged to lung transplant with an 'awake ECMO' strategy when compared to those

managed with conventional mechanical ventilation [13], showing the potential advantages of minimizing sedation. Beyond minimizing sedation, aggressive, early rehabilitation is the next step to potentially further improve outcomes in patients being supported with ECMO as a bridge to lung transplantation [14-16]. This early conditioning is now possible with the introduction of double lumen veno-venous ECMO cannulae and the increasing portability of ECMO technology [14, 17-20].

The safety of rehabilitation on ECMO has now been reported by several centers [15, 16, 21, 22]. While early rehabilitation has been demonstrated to improve outcomes in the setting of critical illness [12, 23-26], the impact of rehabilitation of patients supported with ECMO pre-transplant is unclear. In this report, we describe the impact of increased activity and ambulation on patients supported with ECMO as a bridge to lung transplantation.

Methods

With Institutional Review Board approval, we retrospectively identified all patients who received a lung transplant after bridging support with ECMO at Duke University Medical Center. The medical records of these patients were reviewed with attention to demographics, underlying co-morbidities, hospital course, mechanical ventilation modes and strategies, laboratory values, adjunctive therapies, ECMO course and complications, transplant details, and outcomes including length of stay, health status at discharge, and 1 year survival. ECMO patients who received active rehabilitation and ambulation were compared to those patients who were bridged with ECMO but did not receive pre-transplant rehabilitation. Data between cohorts was compared using Wilcoxon Rank Sums test; p values less than 0.05 were considered significant.

Our rehabilitation protocol has been previously described by Turner, et. al [16]. In brief, rehabilitation began with resistance and stretching exercises, then progressed to sitting, standing, and ultimately, ambulation. Sessions occurred twice per day, as tolerated by the patient. Staffing during these sessions generally consisted of an ECMO specialist, a respiratory therapist, 2 physical therapists, and 1-2 bedside nurses. Each provider was assigned a specific role to ensure safety, including one provider dedicated to support and monitor ECMO cannula position.

Results:

We identified nine consecutive patients who were bridged to lung transplant with ECMO, all between April 2007 and May 2012. Patients receiving rehabilitation during ECMO were transplanted between January 2010 and May 2012.

Pre-transplant health status: Table 1 summarizes key demographic features of the nine transplant recipients included in this study. Primary diagnoses were typical of other patients requiring lung transplantation. Mean age (45 vs. 28, $p = 0.5$) and APACHE III score (57.8 vs. 86.4, $p = 0.3$) were not statistically different between the control cohort (patients 1-4) and the rehabilitation cohort (patients 5-9).   Patients 6, 7, and 8 required high frequency ventilation prior to ECMO cannulation, while patients 6, 8, and 9 demonstrated systemic inflammatory response (SIRS) physiology at time of ECMO cannulation.

ECMO and respiratory support: All patients were bridged to transplant with veno-venous ECMO, and all were managed in either the cardiothoracic intensive care unit (ICU) or pediatric ICU during their ECMO course. Patients in the control cohort were cannulated using a dual cannula technique, using one cannula for venous drainage to the pump and a second cannula for return of oxygenated blood to the patient.   Each patient required at least one femoral vein

cannulation, with a second cannula in either the right internal jugular vein or the other femoral vein. ECMO for these patients utilized the Sorin SCP centrifugal pump (Sorin Groups, Arvada, CO) with a Safeline Quadrox D oxygenator (Maquet Inc., Germany). Patients in the rehabilitation cohort were all cannulated percutaneously via the right internal jugular vein using a single newly-available (19-27 French) dual lumen cannula (Avalon Laboratories, Rancho Domingo, CA), placed with the assistance of either fluoroscopy or transesophageal echocardiography. These patients were maintained on ECMO with a Maquet Rotaflow centrifugal pump (Maquet Inc., Germany) and a Bioline Quadrox D oxygenator (Maquet Inc., Germany).

All nine patients were anticoagulated for ECMO using unfractionated heparin, with goal activated clotting times (ACTs) of 160-180 seconds. The ACT goal was lowered to 140-160 seconds for those patients with tracheostomy or cannula site bleeding (patients 5 and 9). While patients did receive bolus paralytics for procedures (e.g., tracheostomy placement), no patients were maintained on paralytic infusions during their ECMO course. All patients in the control cohort were maintained on MV and sedation while on ECMO awaiting transplant. No formal sedation protocol was used.

No patient had serious complications from ECMO. Patient 1 was noted to have elevated liver enzymes which resolved after transplantation, and patient 7 had a right internal jugular hematoma which was deemed clinically insignificant. Other key ECMO characteristics are summarized in Table 2.

Surgical tracheostomies were placed in control cohort patients within the first 9 days following lung transplantation. In comparison, four of the rehabilitation cohort patients (5, 6, 8,

and 9) received percutaneous tracheostomies prior to lung transplantation within the first 30 hours following ECMO cannulation. Heparin infusion was held approximately 2 hours prior and 2 hours after the procedure for each patient. Patient 5 had moderate superficial bleeding post-procedure and patient 9 required subsequent cauterization of a thyroid laceration, but no other significant complications were noted in any of these four patients post-tracheostomy. Patients 5 and 8 were weaned to humidified oxygen delivered by tracheostomy collar prior to ambulation, while patients 6 and 9 ambulated while connected to a transport ventilator (AVEA VELA ventilator, CareFusion Corp., San Diego, CA; settings: pressure support ventilation, PS 16-18 cm H_2O, PEEP 6-10 cm H_2O, F_iO_2 0.4-0.5). Patient 7 was extubated on ECMO to non-invasive positive pressure ventilation (BiPAP Vision, Philips Respironics, Murraysville, PA; settings: IPAP 12 cm H_2O, EPAP 8 cm H_2O, F_iO_2 0.6) prior to transplantation and did not require a tracheostomy pre- or post-transplant.

Rehabilitation: Nutrition was provided to all patients via gastro-jejunostomy tubes. Patients in the control cohort were sedated for the duration of their support with MV and ECMO and did not participate in physical therapy or rehabilitation during this time. Following ECMO cannulation and stabilization, sedation was minimized for patients in the rehabilitation cohort to allow participation in rehabilitation. Ventilator support was also weaned in these patients, tolerating oxygen saturations greater than 85%.

All patients in the rehabilitation cohort began actively participating with physical therapy within five days of ECMO cannulation, three within the first 48 hours. Four of five patients ambulated on ECMO, with patient 8 ambulating approximately 700 feet (210 meters) and patient 9 ambulating over 1,300 feet (400 meters) in one rehabilitation session. Patient 7 received his transplant early in his ECMO course, after participating in physical therapy (resistance exercises

and sitting on edge of bed) but prior to attempted ambulation. On average, patients receiving rehabilitation received longer courses of MV and ECMO prior to lung transplantation, likely secondary to delayed listing for transplant during the rehabilitation process.

Transplant: Eight patients underwent bilateral orthotopic lung transplant (BOLT). Patient 2 received a lobar transplant due to size mismatch. All patients were supported with ECMO for their lung transplantation, with the exception of patient 4, who was transitioned to cardiopulmonary bypass for the procedure due to surgeon preference. Patient 1 required 4 days of post-transplant ECMO, patients 2 and 8 were decannulated from ECMO at time of transplant, and all other patients were removed from ECMO within 24 hours after transplant. Immunosuppressant protocols were the same for all nine patients.

Outcomes: 1 year survival for patients 1-8 was 100%; patient 9 was alive at the time of this manuscript submission at 4 months post-transplant. Post-transplant length of ventilation, post-transplant ICU length of stay, post-transplant hospital length of stay, total ICU length of stay, and total hospital length of stay were all shorter for patients receiving rehabilitation . Key patient outcomes are summarized in Tables 3 and 4. Patient 4 required resection of an infarcted right middle lobe prior to discharge. Patient 3 died at 50 months post-transplant from colon cancer, patient 5 required single lung re-transplantation for graft failure at 234 days for chronic rejection and died at 16 months post-initial transplantation, and patient 8 died at 17 months post-transplant, also from complications of chronic rejection.

All patients were on room air at discharge, and there were no notable differences in 3 or 12 month FEV_1 values. No patients had focal neurologic deficits at discharge; however, patients 2, 3, and 4 were diagnosed with critical illness neuromyopathy, compared to none of the patients

receiving rehabilitation. Electromyography (EMG) was performed on any patient with concerns for weakness: EMG on patient 2 demonstrated a proximal myopathy, patient 3 a proximal myopathy and polyneuropathy, patient 4 a diffuse myopathy, and normal findings for patient 5. Patient 2 was discharged to an inpatient rehabilitation facility due to her significant deconditioning, while all other patients were discharged home with scheduled outpatient rehabilitation.

Discussion:

Critical illness dramatically decreases the likelihood of successful lung transplantation [4, 7, 27], such that support with MV and/or ECMO are relative contraindications to lung transplantation in some centers [28]. Despite the severity of critical illness in the patients included in this study, 1 year post-transplant survival was 100%, demonstrating that bridging patients to lung transplantation with ECMO may be a viable option for selected critically ill patients with end-stage lung disease. While several other studies have shown success using ECMO as a bridge to transplant [9, 13, 21, 29], this is the first series to show comparison data using a novel rehabilitation and ambulation strategy for these critically ill patients.

This report has several limitations, most notably, the small sample size and retrospective data collection from a single institution. It is difficult to compare subgroups within this population because of potential selection bias, confounders, and small numbers. Of note, four of five rehabilitation patients had cystic fibrosis as the primary diagnosis, compared to one of four patients receiving traditional ECMO. While not statistically different, the rehabilitation patients also had an apparent younger mean age (28 years vs. 45 years), but also had a higher mean APACHE III score (86.4 vs. 57.8) and a longer mean pre-transplant ECMO course (9 vs. 2 days).

As surgical techniques, nutritional support, post-transplant care, immunosuppressant regimens, and other medical management were largely unchanged during this time period, it is feasible the transition to an active rehabilitation approach prior to transplant directly affected the outcome differences seen between these patient groups. The positive effects of pre-transplant conditioning have previously been well documented with patients receiving lung transplantation after prolonged MV [28, 30], suggesting that ECMO patients might experience similar benefits. However, given the number of potential confounders and the cohorts coming from different time periods, it should be noted that clear cause and effect is difficult to ascertain in this case series.

A key consideration in the application of ECMO with rehabilitation as a bridge to lung transplant is patient selection. All patients in this report had single-organ failure and a limited course of critical illness; however, comorbidities including diabetes, bacteremia, and malnutrition were common. The degree of critical illness and organ dysfunction led to the referral of two of the rehabilitation cohort patients to our center after being deemed excessively high-risk by other transplant centers. In each case, it was believed that the patient's mortality approached 100% without initiation of ECMO as a bridge to transplantation. To optimize each patient's lung transplant candidacy, ECMO was initiated as early as possible following intubation using a single cannulation site to allow for maximal mobility and minimize deconditioning.

As transplantable organs are a rare and valuable resource, their utilization must be considered carefully. Two patients in the rehabilitation cohort had bacteremia at the time of ECMO cannulation, and the expectation that infection had to be cleared prior to listing for lung transplant was made clear to the patients' families prior to ECMO cannulation. Additionally,

forthright discussions were held to ensure a clear understanding that listing for lung transplant was contingent upon successful rehabilitation on ECMO.

For the five patients in this study rehabilitated while supported with ECMO, mean time to hospital discharge post-transplant is comparable to the general, non-critically ill lung transplant population [31, 32]. Post-transplant length of stay for these patients was notably shorter than previously reported for those patients supported with MV and/or non-awake ECMO prior to transplantation [6, 30, 33], and potentially shorter than patients supported with 'awake ECMO' prior to transplant [13]. Comparison between the outcomes of our study and the 'awake ECMO' patients reported by Fuehner, et. al. is difficult, as that study used early application of ECMO prior to mechanical ventilation and associated deconditioning, and did not study the effects of active physical therapy and ambulation on this population. When compared to the non-critically-ill lung transplant population at our center, the rehabilitation cohort had similar lengths of mechanical ventilation and ICU stay post-transplant, but slightly extended hospital length of stay.

Despite having longer pre-transplant MV and ECMO courses, patients undergoing rehabilitation were better conditioned than the traditionally managed ECMO patients, as evidenced by the lack of neuromyopathy, improved post-transplant ambulation, and shorter time to ICU and hospital discharge. It seems counterintuitive that prolonged duration of life support for critically ill patients awaiting lung transplant could improve outcomes, but this active rehabilitation program represents a paradigm shift in the management of these complex patients. With a small population of patients, it is difficult to determine what effect this conditioning has on long-term outcomes, however, prior studies have shown a clear relationship between short and long-term outcomes in lung transplant patients [1, 31, 32, 34]. Presumably, reducing post-

transplant ICU and hospital stay will lead to fewer short term-complications and improved long-term outcomes.

Numerous safety concerns must be carefully considered before attempting to rehabilitate patients supported with ECMO [14, 16, 21]. Using a well-coordinated multidisciplinary effort, the patients in this study had no serious complications related to participating in physical therapy and rehabilitation while supported with ECMO. Several other centers have also reported successful ambulation in patients supported with ECMO with minimal complications, both as a bridge to lung transplant and for other causes of respiratory failure [14, 15, 21, 22].

Another important consideration in implementation of a program of this nature is the amount of time spent on the waiting list for transplant. A relatively short wait time on the transplant list may be important for success in these patients given the potential for increased complications related to the prolonged utilization of ECMO. However, in non-ambulatory ECMO patients, successful lung transplantation has been reported after 107 days of ECMO support[35]. Each of the patients in this study received donor lungs within 14 days of being listed for transplant. While this shortened wait time is aided by the level of critical illness, our center's average wait time of 18 days is dramatically shorter than the 150 day average reported for all centers [4]. As such, the use of ambulatory ECMO as successful bridge to lung transplant may not be easily generalizable to centers with longer average wait times.

As we continue to develop our ambulatory ECMO program, increased numbers of patients will provide us a better understanding of the potential benefits and risks of this approach. There are a number of clear challenges and risks associated with ambulating patients supported by ECMO, but the results of this study add to the growing number of reports supporting the

safety of active physical conditioning provided by this novel strategy. Availability of a program of this nature may lead to reconsideration of the lung transplant candidacy of select critically ill patients and also change the overall approach to the management of critical illness in the setting of lung transplantation.

Conclusions:

Bridging critically ill patients to lung transplantation with veno-venous ECMO is a viable treatment option for selected patients. When patients require ECMO support prior to lung transplant, active participation in physical therapy, including ambulation, may provide for a more rapid post-transplantation recovery.

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Table 1: Patient Demographics

Patient	1	2	3	4	5	6	7	8	9
Age (y)	55	51	57	17	16	24	58	20	22
Gender	M	F	M	F	F	F	M	F	F
BMI (On admission)	23.7	29.9	26.6	15.9	16.3	15.5	30.3	19.3	15.8
Primary Diagnosis	Interstitial Pulmonary Fibrosis	Usual Interstitial Pneumonia	Fibrosing Non-specific Interstitial Pneumonia	Cystic Fibrosis	Cystic Fibrosis	Cystic Fibrosis	Interstitial Pulmonary Fibrosis	Cystic Fibrosis	Cystic Fibrosis
Secondary Diagnoses	Diabetes mellitus	Dermato-myositis, hypo-thyroidism	Mixed connective tissue disorder, gastro-esophageal reflux disease	Malnutrition, iron deficiency anemia, diabetes mellitus	Pneumonia, diabetes mellitus, pan-sinusitis	Pneumonia, *berkholderia cepacia* bacteremia, severe deconditioning, chronic obstructive pulmonary disease, diabetes mellitus, pan-sinusitis	Dyslipidemia, hypertension, alcohol abuse, gout, chronic HSV infection	Influenza A, *alcaligenes* bacteremia, hypo-thyroidism, diabetes mellitus	Malnutrition, diabetes mellitus
APACHE III	68	65	51	47	116	97	64	111	44

Table 2: ECMO Characteristics

Patient		1	2	3	4	5	6	7	8	9
Pre-ECMO P/F Ratio		32	90	71	76	103	69	145	69	124
Days of MV prior to ECMO		0.5	1	0.8	0.4	7	3	2	1	1
ECMO days pre-transplant		5	1	0.5	1	8	7	3	14	11
Approximate ECMO 'rest' ventilator settings	Mode	Assist Control	Assist Control	Assist Control	Assist Control	Trach Collar	Support	BiPAP	Trach Collar	Mixed
	Limit	Pressure	Pressure	Pressure	Pressure	---	Pressure	Pressure	---	Pressure
	PIP*	30	18	18	36	---	18	20	---	23
	PEEP#	10	8	8	10	---	6	8	---	10
	F$_i$O$_2$	0.4	0.21	0.21	1.0	1.0	0.4	0.6	1.0	0.5
Typical sedation infusions while on ECMO/		F 50 M 2 D 0.5	F 50 L 2 P 40	F 150 P 50	F 100 M 2	None	None	None	None	None
Rehabilitation		No	No	No	No	Yes	Yes	Yes	Yes	Yes

* Peak inspiratory pressure; # Peak end expiratory pressure;   for sedation infusions, F = fentanyl in mcg/hr, M = midazolam in mg/hr, L = lorazepam in mg/hr, D = dexmetomidate in mcg/kg/hr, and P = propofol in mcg/kg/min.

Table 3: Individual Patient Outcomes

Patient	1	2	3	4	5	6	7	8	9
FEV1 (% predicted) at 3 months [36]	44	Unable to perform	25	38	32	36	42	21	43
FEV1 (% predicted) at 12 months [36]	66	62	43	65	65	70	34	38	N/A
Best FEV1 (% predicted) anytime in the first 12 months [36]	69	63	43	65	65	70	54	53	43
Walking at discharge (feet)	600	N/A	1500	700	1200	1800	300	3500	6000
Total ICU LOS (days)	39	49	60	48	23	25	33	22	30
Total Hospital LOS (days)	51	102	86	151	53	50	63	31	47
Status at Data collection	Alive at 65 months	Died at 50 months	Alive at 54 months	Alive at 47 months	Died at 16 months	Alive at 25 months	Alive at 23 months	Died at 17months	Alive at 4 months