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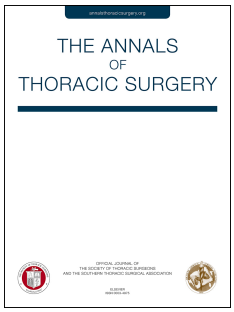

Increasing Opportunity for Lung Transplant in Interstitial Lung Disease with Pulmonary Hypertension

Scott Chicotka, MD, Felipe E. Pedroso, MD, MPH, Cara L. Agerstrand, MD, Erika B. Rosenzweig, MD, Darryl Abrams, MD, Tom Benson, PT, MS, CCS, Aimee Layton, PhD, Daniel Burkhoff, MD, PhD, Daniel Brodie, MD, Matthew D. Bacchetta, MD, MBA

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Increasing Opportunity for Lung Transplant in Interstitial Lung Disease with Pulmonary Hypertension

Running Header: Increasing Lung Transplant Opportunity

Scott Chicotka, MD[1], Felipe E. Pedroso, MD, MPH[1], Cara L. Agerstrand, MD[2], Erika B. Rosenzweig, MD[3], Darryl Abrams, MD[2], Tom Benson, PT, MS, CCS[4], Aimee Layton, PhD[2], Daniel Burkhoff, MD, PhD[5], Daniel Brodie, MD[2*,] Matthew D. Bacchetta, MD, MBA[1*]

1. Section of Thoracic Surgery, Department of Surgery, Columbia University College of Physicians and Surgeons/New York-Presbyterian Hospital, New York, NY.

2. Division of Pulmonary, Allergy and Critical Care, Department of Medicine, Columbia University College of Physicians and Surgeons/New York-Presbyterian Hospital, New York, NY.

3. Division of Pediatric Cardiology, Department of Pediatrics, Columbia University College of Physicians and Surgeons/New York-Presbyterian Hospital, New York, NY.

4. Department of Physical Therapy, Columbia University College of Physicians and Surgeons/New York Presbyterian Hospital Columbia Campus, New York, NY

5. Department of Medicine, Division of Cardiology, Columbia University College of Physicians and Surgeons/New York Presbyterian Hospital Columbia Campus, New York, NY.

*Drs Brodie and Bacchetta are co-senior authors.

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Corresponding Author:

Matthew D. Bacchetta MD

Herbert Irving Pavilion

161 Fort Washington Avenue, Room 336

New York, NY 10032

Email: mb781@cumc.columbia.edu

ABSTRACT

Background: Extracorporeal membrane oxygenation (ECMO) as a bridge to lung transplantation (BTT) for end-stage interstitial lung disease (ILD) and pulmonary hypertension (PH) has varying results based on ECMO configuration. We compare our experience using venovenous (VV) and venoarterial (VA) ECMO BTT for ILD with PH on survival to successful transplantation.

Methods: A single center retrospective review of patients with ILD and secondary PH who were placed on either VV or VA ECMO as BTT from 2010 to 2016. Comparisons for factors associated with survival to transplantation between VV and VA ECMO strategies were made using Cox proportional hazards model. Subgroup analysis included comparisons of VV ECMO patients who remained on VV or were converted to VA ECMO.

Results: A total of 50 patients with ILD and PH were treated initially with either VV (n=19) or VA (n=31) ECMO as BTT. Initial VA ECMO had a significantly higher survival to transplantation compared to initial VV ECMO (p=0.03). Cox proportional hazards modeling showed a 59% reduction in risk of death in VA compared to VV ECMO (HR: 0.41, 95%CI: 0.18-0.92, p=0.03). Patients converted from VV to VA ECMO had significantly longer survival awaiting transplant than those who remained on VV ECMO (p=0.03). Ambulation on ECMO prior to transplantation was associated with an 80% reduction in the risk of death (HR: 0.20, 95%CI: 0.08-0.48, p<0.01).

Conclusions: VA ECMO upper body configuration for patients with end stage ILD and PH significantly improves overall survival to transplantation.

Patients with end stage lung disease have limited options if they decompensate while awaiting lung transplantation. Extracorporeal membrane oxygenation (ECMO) has emerged as a means to bridge patients with significant pre-transplant clinical decline. This strategy may allow for avoidance of, or liberation from, mechanical ventilation, nutritional optimization, and participation in physical therapy, thereby extending the candidacy of critically ill patients for lung transplantation (1-3). This change in the use of ECMO for bridge to transplant (BTT) stands in stark contrast to earlier reports of worse outcomes for patients undergoing lung transplantation while on ECMO (4).

Venovenous (VV) ECMO has been successfully used as bridge to transplant (BTT) in patients suffering from diseases that typically affect gas exchange alone such as cystic fibrosis (CF) or chronic obstructive pulmonary disease (COPD) (5-7). The use of ECMO has increased and expanded to include a range of end-stage lung pathologies such as interstitial lung disease (ILD) (8). Unlike CF and COPD, several studies have reported a high prevalence of some degree of pulmonary hypertension (PH) in patients with ILD, up to 80%, and that the presence of PH associated with ILD (ILD-PH) is an independent risk factor for mortality while waiting for transplant (9-11). Other predictors of mortality in this group include men >60 years old, decreased 6 minute walk distance, decreased % carbon monoxide diffusing capacity, New York Heart Association (NYHA) class III/IV and renal insufficiency (12). In our institution actively listed patients with ILD-PH admitted to our ICU have a 37% pre-transplant mortality, 52% successfully received a transplant, and ECMO was utilized as a BTT in 41% (13). Among those patients who received ECMO as BTT, only 38% survived to transplant, suggesting that clinically decompensated patients with ILD-PH present a significant challenge when using ECMO as a BTT.

The presence of PH may significantly impair cardiac output through right ventricular dysfunction such that VV ECMO may insufficiently support ambulatory and possibly even resting metabolic demands (14). Participation in physical therapy and ambulation during ECMO for BTT has been shown to be safe, and a BTT strategy should involve aggressive early mobilization to prevent deconditioning and potentially improve post-transplant outcomes (15-17), however, this increases physiologic demand on patients with decreased pulmonary function and compromised cardiopulmonary circulation. Depending

on regional specific organ procurement organizations (OPO) average wait times, the BTT time on ECMO can be quite long (18). Thus, ECMO BTT strategies should be aimed at prolonging waitlist survival while minimizing pre-transplant deconditioning by providing adequate physiologic support.

For patients actively listed for lung transplantation with ILD-PH the implementation and optimization of ECMO as BTT has been particularly challenging. We examined the various cannulation strategies and their effects on survival to transplant in an effort to guide future decisions regarding BTT for ILD-PH.

Patients and Methods

This is a retrospective review of a prospectively collected database on patients diagnosed with end-stage ILD with mean pulmonary artery pressure (mPAP) above 25 mmHg, actively listed for lung transplantation, and were treated with VV or VA ECMO as a BTT. Patients with ILD without existing pulmonary hypertension were excluded from this study because there were only two patients with ILD without PH who required ECMO as BTT and thus would not contribute significantly to the study. The primary efficacy outcome was survival to transplantation between the different cannulation strategies. For reference all abbreviations are expanded in Supplemental Table 1. This study was approved by the Columbia University Institutional Review Board (AAAQ6604).

All patients were treated at a single institution from 2010 to 2016. The degree of pulmonary hypertension was directly measured using pulmonary artery catheterization during pre-transplantation evaluation and time from cardiac catheterization to ECMO cannulation was documented (days). Patients were stratified by degree of mPAP into three different subgroups by tertile: mild (25-50 mmHg), moderate (51-80 mmHg), and severe (>80 mmHg).

Patients were cannulated with either VV or VA ECMO configuration based on prior experience and selection algorithm referenced in prior publications from our institution (17). Cannulation was elective or emergent depending on clinical status. Emergent cannulation was performed for acute clinical deterioration with severe hypotension unresponsive to inotropes or hypoxemia unresponsive to maximal

noninvasive or invasive mechanical ventilatory support and adjunctive therapies for severe respiratory failure. All patients requiring ECMO were considered end-stage disease with hemodynamic instability and virtually all patients were requiring inotropic support prior to cannulation. These patients are supported with maximal respiratory therapy to include high flow nasal cannula, non-rebreather mask oxygen, pulmonary vasodilators (inhaled nitric oxide and/or inhaled prostaglandin), with avoidance of intubation/mechanical ventilation whenever possible. To quantify degree of end-organ dysfunction, Simplified Acute Physiology Score (SAPSII) were recorded just before ECMO cannulation and reported in Table 1.

All patients treated with ECMO were managed by a multidisciplinary team including transplant pulmonologists, medical critical care specialists, thoracic surgeons, perfusionists, nurse practitioners, and nurses trained in ECMO. Reasons for failure to receive lung transplant were death while on ECMO or delisting from transplant waitlist. The presence of one or more clinical factors would initiate an overall assessment of patient status and, after a period of time without recovery, would undergo reconsideration of transplant listing. These factors include overall clinical decompensation, renal failure, failure to ambulate, stroke, or cardiac arrest. Over the course of this study period several changes occurred in our ECMO program including prioritization of early physical rehabilitation by a team of physical, occupational and speech therapists experienced in ECMO rehabilitation; incorporation of a pulmonary hypertension specialist into the multidisciplinary team; and increased ECMO training of all staff. The majority of these initiatives occurred after 2013 and in order to better understand the effect of these changes on outcomes, patients were further stratified into two time periods spanning 2010-2013 and 2014-2016.

Surgical Approaches

The decision to cannulate with VV or VA ECMO and when to convert from VV to VA ECMO was made by the multidisciplinary team as previously described by our institution (16) and driven primarily by clinical deterioration or influenced by inability to participate in physical therapy. All

cannula sizes were matched to provide optimal flow to the patient based on predicted cardiac index and the cannula manufacturers' standard flow-pressure curves.

To facilitate early mobilization during BTT, an initial upper body approach for ECMO cannulation was performed if permitted by clinical conditions. VV ECMO cannulation was performed using an Avalon cannula (Maquet, Inc, Wayne, NJ) in the right internal jugular vein using fluoroscopy and trans-esophageal echocardiography guidance as previously described (19). Upper body VA (VA_{UB}) ECMO cannulation was performed using an internal jugular drainage cannula with arterial return cannula inserted into a synthetic graft anastomosed to the axillary artery (Sport Model) or innominate artery (Central Sport Model) as previously described by our institution (20,21). Femoral VA (VA_F) ECMO placed via percutaneous (Seldinger) technique was used to emergently cannulate rapidly decompensating patients. In order to improve early mobilization and reduce differential oxygenation (Harlequin or North/South syndrome), we converted femoral configurations to upper body approaches after patient stabilization ($VA_F \rightarrow VA_{UB}$). Several patients initially cannulated with upper body VV ECMO were converted to upper body VA ECMO ($VV \rightarrow VA_{UB}$) during the study period due to worsening renal function, exercise intolerance, or signs of worsening right heart function on VV ECMO while awaiting lung transplantation.

Statistical Analysis

Patient demographics were compared for VV and VA ECMO strategies. Categorical variables were compared using Chi-Squared and Fischer's exact test. Continuous variables were reported as mean ± standard deviation (SD) or median and interquartile range (IQR). Continuous variables were compared using two sample t-Test and Wilcoxon Mann-Whitney test. Survival analysis comparing individuals initially cannulated using VV and VA ECMO strategies was performed in an intention-to-treat analysis using Kaplan Meier methods and log rank test. Within each ECMO strategy group, comparisons were made between patients who were successfully transplanted and those who died while awaiting transplantation. We assessed differences in demographics between VV ECMO and $VV \rightarrow VA_{UB}$ ECMO

groups. Outcome measures between these groups were also performed that included survival analysis to assess the impact of ECMO conversion as well as between those who were initially cannulated via VA_{UB} to those in the $VA_F \rightarrow VA_{UB}$ ECMO group. To assess for differences during treatment periods (2010-2013 vs. 2014-2016), patients were dichotomized by treatment period and comparisons between patient demographics and outcomes were performed.

There is a sense of urgency to find an acceptable donor lung for ECMO BTT patients, which raises the concern for the potential impact on donor criteria. More stringent selectivity could lead to longer wait times on ECMO while less stringent criteria may decrease donor lung quality and lead to worse post transplant survival. Donor age and status (standard criteria (SCD) vs. extended criteria/high risk (ECD/HR)) were used to compare selectivity, as a surrogate for quality of accepted donor lungs vs. urgency to transplant, between overall VV and VA ECMO groups and within VA ECMO conversion subgroups.

In order to evaluate factors associated with pre-transplantation mortality, we completed a Cox proportional hazards model. All variables that were potential risk factors associated with death while awaiting transplantation were assessed. Factors that were significant or clinically relevant were included in the final Cox proportional hazards model in order to assess association with death while awaiting transplantation. The proportional hazards assumption was tested using Schoenfeld residual method.

All statistical analyses were performed using STATA version 14.1 (StataCorp. College Station, Tx. 2016) and a p-value of less than 0.05 was considered significant.

Results

Overall Patient Cohort

There were a total of 50 patients (25 male, 25 female) with a mean age of 48.6 ± 13.4 years, Lung Allocation Score (LAS) of 89.7 ± 6.4, mean mPAP of 72.2 $\pm$ 4.6mmHg, and time from pulmonary artery

catheterization to ECMO was 259 ± 248 days in this study. Mean pre-transplantation duration of ECMO was 22.5 ± 23.0 days. A total of 19 and 31 patients underwent initial VV and VA cannulation strategies, respectively. A total of 7 patients in the VV ECMO group and 20 patients in the VA ECMO group survived to transplant, the overwhelming majority (98%) received double lung transplant. Of the patients who survived to transplantation, the vast majority of patients remained on their pre-op ECMO configuration during lung transplant surgery. Comparing between VV and VA ECMO strategies, cardiopulmonary bypass (CPB) was utilized in VV group vs. VA group (3 (42%) vs. 3 (15%) p=0.336). There were no differences in donor lung quality between VV and VA ECMO groups with regard to donor age (39.1 ± 16 years vs. 35.6 ± 17.5 years p=0.71) or with regard to donor status for ECD/HR (66% ECD/HR for VV vs. 71% ECD/HR for VA p=0.201). The VA ECMO group had a significantly higher baseline pre-ECMO mPAP compared to the VV ECMO group (81.9 ± 32.1mmHg vs. 56.4 ± 26.2mmHg, p=0.01). A greater proportion of VV patients received tracheostomy while awaiting transplantation (42.1%) versus VA patients (9.7%, p=0.01). There were no significant differences in patient demographics in those who were transplanted or deceased while awaiting transplantation within the VV ECMO group. A significantly greater proportion of VA ECMO patients who were transplanted ambulated prior to transplantation as compared to those who died while awaiting transplantation (95% vs. 45%, $P < 0.05$). (Table 1)

There were no significant differences in age, gender, body mass index (BMI) (kg/m^2), time on ECMO, LAS, mPAP, ambulation status, or requirement for tracheostomy between those patients placed on ECMO in 2010-2013 vs. 2014-2016. The only differences between these two treatment periods were the proportion of patients initially cannulated on VA ECMO (75.7% in 2014-2016 vs. 23.1%, in 2010-2013 $p < 0.01$) and the amount of time on ECMO after transplantation (3.2 ± 2.5 in 2014-2016 vs. 0.6 ± 1.2 in 2010-2013, p=0.01). (Supplemental Table 2)

Conversion Analysis: VV→VA_{UB} and VA_F→ VA_{UB}

Comparisons of VV ECMO patients who remained on VV ECMO to VV→VA_{UB} showed patients in the VV→ VA_{UB} ECMO group were able to stay on ECMO for more days as compared to those who remained on VV ECMO (31.29 ± 14.29 vs. 7.83 ±7.47, p<0.001) (Supplemental Table 3). Within the VA ECMO group, patients who were initially cannulated to VA_{UB} compared to VA_F→ VA_{UB} showed that relative to patients who were initially cannulated VA_{UB}, VA_F→ VA_{UB} patients had a significantly greater number of post-transplant days on ECMO (4.6 ± 2.4 vs. 1.9 ± 2.0, p=0.01) and a longer length of stay post transplantation (49.6 ± 30.0 vs. 28.5±15.8, p=0.05) (Supplemental Table 4). Additionally there were no differences in donor lung quality between VA_{UB} compared to VA_F→ VA_{UB} with respect to donor age (32.3±17.8 years vs. 39.1±17.5 years p=0.45) and donor status (36% ECD/HR for VA_{UB} vs. 44% ECD/HR for VA_F→ VA_{UB} p=0.981).

Survival of VV vs. VA ECMO

On Kaplan Meier survival analysis, overall survival while awaiting transplantation was significantly greater in those patients initially cannulated on VA ECMO as compared to VV ECMO (p=0.025) (Figure 1). Within the VV ECMO cannulation group, those who were converted to VA ECMO had a significantly longer waitlist survival time while awaiting transplantation as compared to those who remained on VV ECMO (p=0.025) (Figure 2).

Risk of Death While Awaiting Transplantation

In univariate cox proportional hazards modeling, gender, age, BMI, LAS, treatment period, and mPAP showed no significant effect on the risk of death while awaiting transplantation. However, in univariate analysis, VA ECMO patients exhibited a 59% reduction in the risk of death as compared to VV ECMO patients (Hazard Reduction (HR) 0.41, 95%CI: 0.18-0.92, p=0.03). Additionally, there was an 80% reduction in the risk of death while awaiting transplantation in those patients who ambulated prior to transplantation compared to those who did not (HR 0.2, 95%CI: 0.08-0.48, p<0.01). Finally, there was a

trend for an increase in the risk of death while awaiting transplantation in those patients that exhibited a complication while on ECMO (HR: 2.44, 95%CI: 0.96-6.19, p=0.06). (Supplemental Table 5).

The final cox proportional hazards model included ECMO Strategy (VA vs. VV), ambulation status (Yes vs. No) and Complication on ECMO (Yes vs. No). Our final model showed a 66% reduction in the risk of death while awaiting transplantation in the VA ECMO group as compared to the VV ECMO group (HR 0.34, 95%CI: 0.15-0.81, p=0.015) when adjusting for those who ambulated prior to transplantation and had a complication while on ECMO (Supplemental Table 5).

Complications

Complications resulting from ECMO cannulation were seen in 24% of the total cannulations. Comparison between the VV and VA ECMO groups demonstrated no differences overall VV (21.1%) vs VA (25.8 %) p=1.00. The complications experienced in the VV ECMO group were bleeding (2), infection (1), and stroke (1) while the complications in the VA ECMO group were limb ischemia (3), stroke (2), acute renal failure (1), bleeding (1), and arterial injury during cannulation requiring repair (1). Within the VV ECMO groups there were no complications within the group who survived to transplant while 33% of the patients that did not survive to transplant experienced a complication related to ECMO (p=0.245). While this was not statistically significant the low numbers in these groups does not allow us to conclusively say that no difference exists between these groups. Within the VA ECMO group complications related ECMO were experienced in 27% who did not survive to transplant vs. 25% that did survive to transplant (p=1.00) (Table 1).

Comment

The use of ECMO as BTT is increasing as outcomes for its use improve for a wide variety of conditions (6-8). A significant proportion of patients with ILD have associated PH, and the presence of PH in these patients is an independent risk factor for pre-transplant mortality (10,11). There is a notably different response to mechanical circulatory support in patients with end stage ILD-PH, which may be in

part due to the presence of right ventricular strain and reduced cardiac output. Many ILD-PH patients require mechanical circulatory support for an extended period of time and we have observed important differences in outcomes between patients treated with VV and VA ECMO. These differences are exacerbated in our particular regional OPO because of the high LAS and long transplant waitlist times (22–24).

We found that ILD-PH patients initially cannulated with VV ECMO had decreased survival to transplantation compared to those initially cannulated with VA ECMO with no difference in donor lung selectivity based on donor age or status. Within the VV ECMO group there was no difference in survival to transplant based on severity of PH (Table 1). These findings suggest that right heart failure may play a more prominent role in the decompensation of these patients rather than simply worsening of diffusion and ventilation capacity. In the decompensating ILD patient, VV ECMO may provide adequate gas exchange and reduce pulmonary hypoxic vasoconstriction with resulting right ventricular unloading, but it does not compensate entirely for increased pulmonary vascular resistance nor does it decompress or offload the failing right ventricle. A recent report that utilized primarily a VV ECMO strategy in these patients also found that the presence of right ventricle (RV) dysfunction in ILD is a risk factor for death for patients undergoing BTT (10). In our analysis, ILD-PH patients supported only with VV ECMO had decreased waitlist survival to transplant, particularly with BTT wait time greater than 20 days (Figure 1). This suggests that VV ECMO provides a transient compensation in oxygenation while RV function worsens possibly owing to fibrotic compression of the pulmonary vasculature and vasculopathy that persists despite VV ECMO support. We also found that these VV ECMO supported patients often had significantly higher rates of tracheostomy in order to improve oxygen delivery and permit participation in physical therapy.

VV→ VA_{UB} patients survived significantly longer while awaiting transplantation than patients maintained on only VV ECMO however, this had little impact on survival to transplantation. An inherent problem with a strategy dependent upon conversion from VV→VA_{UB} ECMO to provide sufficient physiologic support is that many of these patients were not ambulating for a significant period of time and

hence required more time to recover on VA ECMO after conversion. Prolonged periods of immobility in this patient population increases pre-transplant deconditioning and neuromuscular weakness and have been associated with worse post lung transplant outcomes (15,16). In our cohort the average time to conversion VV→VA_{UB} ECMO was 5.4 days. When adjusting for ECMO cannulation strategy, our Cox proportional hazards model revealed that patients who ambulated while on ECMO had significantly lower risk of pre-transplant death, suggesting that even temporary periods of immobility associated with a strategy of VV→VA_{UB} ECMO could be associated with decreased survival.

ILD-PH patients initially cannulated with VA ECMO, although at higher baseline risk of mortality due to significantly higher mPAP, had a significant survival benefit and hence were able to remain on the transplant waiting list for longer durations. ILD-PH patients on VA ECMO were also more likely to ambulate, further improving survival to transplant. We speculate that the RV unloading and improved forward flow from the upper body VA ECMO configuration provided better physiologic and more durable support than VV ECMO, which is consistent with our simulation modeling (14).

There were no differences in outcomes when comparing patients who underwent VA_F→ VA_{UB} with those cannulated directly to VA_{UB} ECMO. The average time to conversion to VA_{UB} ECMO was 2.9 days with no apparent effect on pre-transplant survival. This suggests either a two-stage or single stage (direct to VA_{UB}) approach can be utilized based on patient stability provided there is an early conversion to VA_{UB} ECMO to minimize immobility time. Post-transplant, there was no difference in time to discharge between the VV and VA ECMO groups and all patients who were successfully bridged to lung transplant survived to discharge.

This study is limited by its retrospective design and single center experience, although this is the largest published cohort of ILD-PH as BTT. The time period over which the study took place also may have influenced differences in outcomes. Prior to 2014 we predominantly cannulated ILD-PH patients with VV ECMO. Anecdotal observations of poor initial outcomes with VV ECMO and development of a more durable VA_{UB} cannulation strategy (20) led us to try alternate approaches such as VV→VA_{UB} ECMO, and direct cannulation to VA_{UB} ECMO later in the study. Thus, over the study period there was a

shift in preference to VA_{UB} ECMO cannulation. Additionally, we adjusted our practices to improve patient management. The extent to which these cannulation strategies and systematic changes affected the outcomes cannot truly be determined. For this study the measurements of mPAP were performed at right heart catheterization during transplant workup, which was often many months before clinical deterioration and likely underestimated the actual mPAP at time of ECMO cannulation and BTT. Ambulation data in the study was collected in binary form; that is, if the patient walked at any time during their ECMO BTT this was counted as positive for ambulation. This method does not provide a nuanced index of the quantity or intensity of ambulation and rehabilitation, which is intended to prevent deconditioning.

Conclusion

Despite the increased risk of death for ILD-PH patients in our OPO due to long wait times, this risk could be modified with ECMO BTT. Regardless of the severity of PH, VA_{UB} ECMO provided more durable support compared to VV ECMO. VA_{UB} ECMO prevents pre-transplant deconditioning by improving ambulation, decreases the need for tracheostomies for mechanical ventilator support, and prolongs survival to transplantation. The choice of cannulation strategy is critical in this patient population and cannulation to VA_{UB} ECMO should be considered as the initial approach in decompensating ILD-PH patients.

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25. **Table 1: Patient Demographics Venvenous (VV) vs. Venoarterial (VA) Extracorporeal Membrane Oxygenation (ECMO)**

		Total	VV	VA	P-Value*	VV ECMO		P-Value*	VA ECMO		P-Value*
						Transplanted	Deceased		Transplanted	Deceased	
Number of Patients		50	19	31		7	12		20	11	
Gender	Male	25	10	15	1.00	4	6	1.00	10	5	1.00
	Female	25	9	16		3	6		10	6	
Age	Mean ± S.D.	48.6 ± 13.4	51.0 ± 11.1	47.1 ± 14.6	0.32	49.6 ± 14.0	51.8 ± 9.6	0.68	48.3 ± 12.3	44.9 ± 18.7	0.55
Body Mass Index (Kg/m^2)	Mean ± S.D.	24.3 ± 5.1	23.7 ± 5.4	24.7 ± 5.0	0.52	24.1 ± 5.6	23.5 ± 5.4	0.82	25.8 ± 4.4	22.7 ± 5.5	0.10
Time on ECMO	Mean ± S.D.	22.5 ± 23.0	16.5 ± 15.4	26.1 ± 26.2	0.15	9.0 ± 8.6	20.8 ± 17.1	0.11	30.1 ± 30.9	19 ± 13.0	0.26
	IQR	2 - 49	3 - 30	5 - 49		6 - 6	9 - 30		7 - 49	10 - 23	
Lung Allocation Score	Mean ± S.D.	89.7 ± 6.4	91.2 ± 8.0	88.7 ± 5.1	0.18	90.1 ± 9.6	91.9 ±7.4	0.66	88.7 ± 5.9	88.7 ± 3.4	0.97
Mean Pulmonary Artery Pressure (mPAP)[a]	Mild	17	10	7	0.06	4	6	1.00	6	1	0.26
	Moderate	14	5	9		2	3		4	5	
	Severe	19	4	15		1	3		10	5	

Mean PAP	Mean ± S.D.	72.2 ± 4.6	56.4 ± 26.2	81.9 ± 32.1	0.01	54.3 ± 25.4	57.7 ± 27.8	0.80	78.9 ± 32.5	87.4 ± 32.1	0.49
Ambulation Status	Yes	37	13	24	0.52	6	7	0.33	19	5	<0.05
	No	13	6	7		1	5		1	6	
Required Tracheostomy	Yes	11	8	3	0.01	3	5	1.00	0	3	0.04
	No	39	11	28		4	7		20	8	
Post Transplant ECMO Time (Days)	Number Pts	27	7	20	0.03	7	-	-	20	-	-
	Mean ± S.D.	2.4 ± 2.5	0.7 ± 1.3	3.0 ± 2.5		0.7 ± 1.3	-	-	3.0 ± 2.5	-	
	IQR	0 - 5	0 - 0	0 - 5		0 - 0	-	-	0 - 5	-	
Transplant to Discharge Time (Days)	Number Pts	27	7	20	0.43	7	-	-	20	-	-
	Mean ± S.D.	35.0 ± 4.2	29.3 ± 11.7	37.0 ± 24.3		29.3 ± 11.7	-	-	37.0 ± 24.3	-	
	IQR	18 - 50	31 - 31	19 - 50		31 - 31	-	-	19 - 50	-	
Cath to Cannulation Time (Days)	Mean ± S.D.	259 ± 248.9	274.4 ± 262.2	249.6 ± 244.4	0.74	253.3 ± 120.5	286.8 ± 322.6	0.80	231.7 ± 254.7	282.1 ± 232.8	0.59
	IQR	67 - 347	66 - 371	687 - 314		197 - 367	59 - 575		63.5 - 296.5	67 - 587	
Simplified Acute	Mean ± S.D.	30 ± 9.9	32.8 ± 11.6	28.3 ± 8.6	0.12	29.3 ± 10.9	34.8 ± 11.9	0.33	26.9 ± 8.5	30.7 ± 8.6	0.25

Physiology Score 2	IQR	23 - 38	23	21 - 34		22 - 38	28 - 38		20 - 33.5	22 - 40	
ECMO Complications[d]	Yes	12	4	8	1.00	0	4	0.25	5	3	1.00
	No	38	15	23		7	8		15	8	

Note: IQR = Interquartile Range; PAP = Pulmonary Artery Pressure

* Categorical Variables: Fischer's Exact test, Continuous Variables : Two Sample T-Test

[a] Mean Pulmonary Artery Pressure (mPAP) = Mild (mPAP < 50), Moderate (mPAP 51 - 80), Severe (mPAP > 80)

[b] Ability to ambulate prior to transplantation.

[c] Simplified Acute Physiology Score 2: Assessed prior to ECMO cannulation.

[d] ECMO Complications: Limb ischemia, neurologic injury, acute renal failure, bleeding, infection, arterial injury requiring repair.

Figure Legend

Figure 1. Opportunity for transplantation: Kaplan Meier curves evaluating overall survival in all patients initially supported with VA versus VV ECMO.

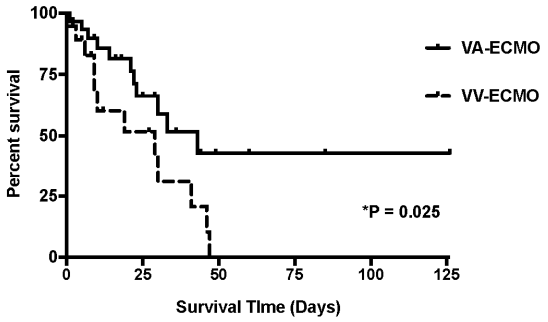
Figure 2. Opportunity for transplantation: Kaplan Meier curves evaluating overall survival in VV ECMO patients who remained on VV ECMO compared to those that were VV→VA_{UB} ECMO.

Acronym Expansion

Acronym	Expansion
ECMO	Extracorporeal Membrane Oxygenation
BTT	Bridge to Transplant
ILD	Interstitial Lung Disease
PH	Pulmonary Hypertension
VV	Veno-Venous
VA	Veno-Arterial
CF	Cystic Fibrosis
COPD	Chronic Obstructive Pulmonary Disease
ILD-PH	Interstitial Lung Disease with Pulmonary Hypertension
ICU	Intensive Care Unit
OPO	Organ Procurement Organization
mPAP	Mean Pulmonary Artery Pressure
SAPS II	Simplified Acute Physiology Score
VAUB	Upper Body Veno-Arterial
VAF	Femoral Veno-Arterial
VAF →VAUB	Femoral Veno-Arterial converted to Upper Body Veno-Arterial
VV →VAUB	Veno-Venous converted to Upper Body

	Veno Arterial
SD	Standard Deviation
IQR	Interquartile Range
LAS	Lung Allocation Score
CPB	Cardiopulmonary Bypass
BMI	Body Mass Index
HR	Hazard Reduction
RV	Right Ventricle

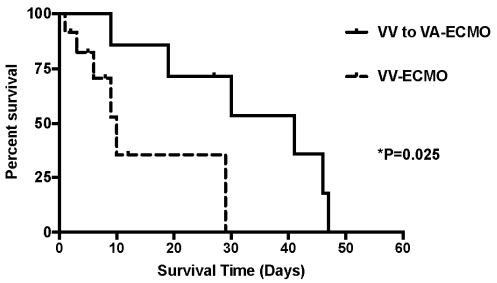
Opportunity for Transplantation
Overall Survival waiting for transplanation
Venoarterial (VA) vs. Venovenous (VV).



No. at Risk						
VV-ECMO	19	6	0	0	0	0
VA ECMO	31	11	3	2	1	1

*Comparisons by Log Rank Test

Opportunity for Transplantation
(Overall Survival waiting for transplanation)
Continued Veno-Venous (VV) ECMO compared to converted to VA-ECMO.



NO. at Risk						
VV to VA-ECMO:	7	6	5	4	3	0
VV-ECMO:	12	3	1	0	0	0

*Comparison by Log Rank Test.