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Morbidity of conversion from venovenous to venoarterial ECMO in neonates with meconium aspiration or persistent pulmonary hypertension☆

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ABSTRACT

Background: Outcomes in neonates receiving extracorporeal membrane oxygenation (ECMO) for meconium aspiration syndrome (MAS) and/or persistent pulmonary hypertension (PPHN) are favorable. Infants with preserved perfusion are often offered venovenous (VV) support to spare morbidities of venoarterial (VA) ECMO. Worsening perfusion or circuit complications can prompt conversion from VV-to-VA support. We examined whether outcomes in infants requiring VA ECMO for MAS/PPHN differed if they underwent VA support initially versus converting to VA after a VV trial, and what factors predicted conversion.

Methods: We reviewed the Extracorporeal Life Support Organization registry from 2007 to 2017 for neonates with primary diagnoses of MAS/PPHN. Propensity score analysis matched VA single-runs (controls) 4:1 against VV-to-VA conversions based on age, pre-ECMO pH, and precannulation arrests. Primary outcomes were complications and survival. Data were analyzed using Mann–Whitney U and Fisher's exact testing. Multivariate regression identified independent predictors of conversion for VV patients.

Results: 3831 neonates underwent ECMO for MAS/PPHN, including 2129 (55%) initially requiring VA support. Of 1702 patients placed on VV ECMO, 98 (5.8%) required VV-to-VA conversion. Compared with 364 propensity-matched isolated VA controls, conversion runs were longer (190 vs. 127 h, $P < 0.001$), were associated with more complications, and decreased survival to discharge (70% vs. 83%, $P = 0.01$). On multivariate regression, conversion was more likely if neonates on VV ECMO did not receive surfactant (OR = 1.7;95%CI = 1.1–2.7;P = 0.03) or required high-frequency ventilation (OR = 1.9;95%CI = 1.2–3.3;P = 0.01) before ECMO.

Conclusion: Conversion from VV-to-VA ECMO in infants with MAS/PPHN conveys increased morbidity and mortality compared to similar patients placed initially onto VA ECMO. VV patients not receiving surfactant or requiring high-frequency ventilation before cannulation may have increased risk of conversion. While conversions remain rare, decisions to offer VV ECMO for MAS/PPHN must be informed by inferior outcomes observed should conversion be required.

Level of evidence: Level of evidence 3
Retrospective comparative study.

Extracorporeal membrane oxygenation (ECMO) is a widely accepted modality for the treatment of critically-ill neonates suffering from reversible cardiac or respiratory insufficiency refractory to conventional medical therapy. Patients are offered either venoarterial (VA) or venovenous (VV) ECMO based on the presence of combined cardiac and respiratory failure (VA), versus isolated pulmonary failure with preserved cardiac function (VV). Persistent pulmonary hypertension of the newborn (PPHN) and meconium aspiration syndrome (MAS) represent two neonatal diagnoses associated with the most favorable ECMO outcomes [1], and will often be amenable to VV support [2,3]. Neonatal providers generally encourage the use of VV ECMO whenever possible owing to several well-described advantages of this modality, namely the avoidance of carotid artery occlusion, the preservation of pulsatile

Abbreviations: ECMO, extracorporeal membrane oxygenation; ELSO, Extracorporeal Life Support Organization; VA, venoarterial; VV, venovenous; PPHN, persistent pulmonary hypertension; MAS, meconium aspiration syndrome.

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systemic circulation, and the maintenance of right ventricular preload and pulmonary blood flow [4,5].

Despite its purported advantages, VV ECMO may not offer sufficient support in the face of a child's worsening hemodynamics. Additionally, since neonatal VV ECMO is reliant on the precise position and orientation of a double-lumen VV cannula, flow disturbances secondary to a tenuous cannula may further compromise the efficacy of a given VV ECMO run [6–9]. In such instances, conversion to VA ECMO may be required. There are minimal data available that describe the frequency, predisposing factors, and outcomes for neonates who require an unanticipated conversion from VV to VA ECMO. This study explores the impact of this conversion in a population of patients with high VV utilization and generally favorable outcomes, namely neonates with PPHN or MAS. We hypothesized that VV-to-VA conversion may negatively influence outcomes compared to infants maintained on a single modality of support, and sought to both understand the differential outcomes when conversion is required as well as characterize the factors that may be predictive of converting from VV to VA ECMO.

1. Methods

We reviewed deidentified data from Extracorporeal Life Support Organization (ELSO) registry from 2007 to 2017 for all newborns less than 28 days old who required ECMO with a primary diagnosis of MAS or PPHN based on select ICD-9 (770.1, 763.84, 777.1, 770.11, 770.12, 747.89, 747.83, 416.0) and ICD-10 (P24.9, P03.82, P03.82, P24.00, P24.01, Q28.8, P29.3, I27.0) codes. The study did not qualify for review by the NYU Langone Health Institutional Review Board based on institutional policies regarding analysis of deidentified data, in conjunction with the ELSO Data Use Agreement which authorizes the sending and receiving of deidentified data sets between institutions. Data are reported to the ELSO Registry by 823 active ECMO centers using a standardized online registry which comprehensively documents various patient, treatment, and outcome-related variables. Registry cases excluded from analysis included patients who underwent distinct 2nd or 3rd ECMO runs (in contrast to VV-to-VA conversions within a single run), patients utilizing the veno-venoarterial (V-VA) mode of ECMO, and patients for whom the mode of ECMO was documented as 'other' or 'unknown'.

Variables selected for analysis included gestational age, weight, Apgar scores, age at cannulation, secondary diagnoses, pre/post-ECMO arterial blood gas values, pre/post-ECMO ventilator settings, pre/post-ECMO hemodynamics, pre-ECMO cardiac arrest, pre-ECMO pharmacologic support, ECMO flow rates, duration of ECMO, ECMO cannulae and ECMO circuit equipment. Primary outcome measures were ECMO complications and survival. Complications are coded according to ELSO registry-defined categories: mechanical, hemorrhagic, neurological, renal, cardiovascular, pulmonary, limb, infectious, and metabolic. Prior to comparative analyses, continuous variables were individually evaluated for distribution normality using a Shapiro–Wilk statistic and normality plots to guide nonparametric testing.

Two phases of comparative data analyses were performed. First, outcomes of neonates undergoing VV-to-VA conversion were compared to data from neonates undergoing isolated VA ECMO runs. Propensity score matching [10] was undertaken using a logistic regression model that included the variables of age at cannulation, pre-ECMO pH, and precannulation arrest status. Matching variables were selected after assessing all precannulation continuous and categorical variables for sufficient discriminatory variation across cohorts, combined with their clinical relevance to a clinician making a real-time decision at the bedside on which modality of ECMO to offer. Model variables were restricted to those with the greatest variance and strongest clinical relevance to avoid dilution of the propensity scoring with less meaningful variables. Similar clinical-applicability approaches for the selection of propensity score variables are described in a variety of published studies on ECMO outcomes [11–14]. Propensity score analysis successfully matched VA single-runs (controls) 4:1 against VV-to-VA conversions. After matching, data across these two cohorts were then analyzed using Mann–Whitney U and Fisher's exact testing.

In the second phase of analysis, we focused on the subgroup of patients initially offered VV support to construct a multivariate regression model for identifying independent predictors of VV-to-VA conversion. Parameters holding the strongest relationships with the dependent variable (VV-to-VA conversion) were identified as candidate predictors by univariate two-tailed Fisher's exact or Mann–Whitney U testing ($P < 0.2$). Candidate predictors were then entered according to their univariate significance into a stepwise (forward selection — to enter strongest variable correlations earlier into the model) regression model against the dependent variable. Coefficients bearing multivariate statistical significance predictive of the dependent variable were included in the final models after assessment for collinearity. Results containing continuous variables are presented as median values with interquartile ranges unless otherwise noted. Statistical significance was assumed at $P < 0.05$. Data analyses were performed using the IBM Statistical Package for the Social Sciences (IBM SPSS 25.0, IBM, Armonk, NY).

2. Results

After excluding second and third ECMO runs as well as ineligible modes of support, we identified 3831 neonates who underwent ECMO for MAS/PPHN over the 10 year study period. These included 2129 (56%) initially requiring VA ECMO and 1702 neonates who were initially placed on VV (44%) support. ECMO survival and survival to discharge for the entire study population were 92% and 85%, respectively. Among those patients who initially required VV support, 98 (5.8%) required VV-to-VA conversion. These conversion events appeared randomly distributed across the study period, and did not cluster around a certain time-interval nor did they demonstrate a statistically-appreciable trend over time (Table 1). Within this conversion cohort, 80 neonates (82%) survived ECMO and 69 patients (70%) survived to discharge. Assessment of all available patient, equipment, and treatment related variables for the conversion subgroup only identified pO2 at 24 h postcannulation and the development of neurologic complications as having statistically significant associations with ECMO survival (Table 2). Intracranial hemorrhage represented the most common neurologic complication observed among the nonsurvivors of VV-to-VA conversion (7 of the 9 patients with neurologic complications).

Of the 98 VV-to-VA conversions identified, 17 neonates (17%) initially underwent dual-site venous cannulation versus 81 neonates (82%) who received a double lumen cannula for the initial VV run, only 10 (12%) of which employed a bicaval Avalon® cannula. The configurations which comprised dual-site venous cannulations in this conversion cohort included 9 patients with right internal jugular (IJ) + right femoral venous access, 6 patents with right IJ + right atrial ac-

Table 1
Trends over time in VV and VA ECMO, and VV-to-VA conversions in neonates with MAS/PPHN.

Year	Number of VV to VA Conversions	VV ECMO runs (%)[a]	VA ECMO runs (%)[a]
2007	10	183 (48%)	196 (52%)
2008	8	170 (45%)	210 (55%)
2009	14	173 (48%)	184 (52%)
2010	9	205 (53%)	184 (47%)
2011	7	169 (45%)	206 (55%)
2012	13	160 (44%)	207 (56%)
2013	9	156 (44%)	202 (56%)
2014	18	169 (42%)	233 (58%)
2015	8	143 (42%)	201 (58%)
2016	2	99 (37%)	171 (63%)
2017	0	75 (36%)	135 (64%)

[a] Percentages reflect relative proportion of all VV vs. all VA runs in MAS/PPHN patients for the given year.

Table 2
Impact of clinical factors on ECMO survival in 98 neonates requiring VV to VA conversion.

	Failed to recover ($N = 18$)	Survived ECMO ($N = 80$)	P
Pre-ECMO variables			
Female gender	10 (56%)	32 (41%)	0.30
Weight (kg)[a]	3.3 (2.9–3.8)	3.4 (3.1–3.9)	0.27
Gestational age (weeks)[a]	40 (39–41)	40 (39–41)	0.95
Age at cannulation (days)[a]	2 (1–5)	1.5 (1–3)	0.47
High frequency ventilation	11 (69%)	57 (79%)	0.51
Vasopressors or inotropes	10 (56%)	45 (57%)	0.99
Neuromuscular blockers	8 (44%)	52 (66%)	0.11
Systemic steroids	3 (17%)	6 (7.6%)	0.36
Inhaled nitric oxide use	14 (78%)	73 (92%)	0.09
Surfactant administered	5 (28%)	26 (33%)	0.78
Lowest pre-ECMO pH[a]	7.28 (7.15–7.37)	7.20 (7.16–7.30)	0.52
Pre-ECMO hand-bagging	3 (17%)	5 (6.5%)	0.17
Pre-ECMO arrest	1 (5.6%)	6 (7.5%)	0.99
ECMO support variables			
Duration of ECMO (h)[a]	253 (85–458)	189 (123–270)	0.41
Percutaneous cannulation	4 (22%)	10 (13%)	0.28
Avalon cannula used	3 (17%)	7 (8.8%)	0.39
Double lumen cannula replaced	6 (33%)	29 (36%)	0.99
Hollow fiber oxygenator[b]	7 / 9 (78%)	24 / 35 (69%)	0.70
Centrifugal/nonroller pump[b]	3 / 9 (33%)	12 / 34 (35%)	0.99
Hemofilter used	4 (22%)	13 (16%)	0.51
Best pO2 (torr) 24 h on ECMO[a]	59 (51–65)	80 (63–112)	0.008
Post-ECMO variables			
Mechanical complication	10 (56%)	49 (61%)	0.79
Hemorrhagic complication	9 (50%)	23 (29%)	0.10
Neurologic complication	9 (50%)	11 (14%)	0.002
Renal complication	6 (33%)	23 (29%)	0.78
Cardiovascular complication	13 (72%)	52 (65%)	0.78
Pulmonary complication	6 (33%)	11 (14%)	0.08
Infectious complication	0 (0%)	4 (5.0%)	0.99
Metabolic complication	6 (33%)	20 (25%)	0.56

[a] Data presented as medians with interquartile range.
[b] Reflects different denominator for cohort owing to missing data points in ELSO registry.

cess, and 2 patients with right IJ + right IJ cephalad access. Upon converting to VA ECMO, 35 patients (43%) had their double lumen cannula completely replaced by a single lumen drainage cannula. These 35 patients did not demonstrate a different rate of neurologic complications compared to neonates who did not have their VV cannula replaced (14% vs. 24%, P = 0.31). Conversion to VA ECMO nearly universally involved cannulation of the right common carotid artery, except for one case which utilized the aorta. Only 14 conversion patients (14%) underwent a percutaneous cannulation at some point during their ECMO course, with percutaneous access occurring at similar rates for both single-site dual-site initial VV cannulations. The timing and reasons for conversion from VV to VA ECMO are not captured by registry data, making it impractical to query relationships between cannulation data and their relative impact on VV-to-VA conversion.

The first phase of comparative analysis investigated differential outcomes between patients who were offered VA ECMO up front, versus those who converted to VA ECMO after an unsuccessful initial VV course. Propensity score matching on select precannulation variables identified a cohort of 364 isolated VA ECMO runs to serve as a control group against the 98 VV-to-VA conversion cases (4:1 matching). Neonates requiring VV-to-VA conversion underwent a longer median ECMO run compared to patients remaining on isolated VA support throughout their ECMO course (190 h vs. 127 h, P < 0.001). Conversion runs demonstrated lower rates of ECMO survival (82% vs. 93%, P = 0.002) and survival to discharge (70% vs. 83%, P = 0.01) compared to solitary VA runs. Additionally, we observed higher complication rates in the VV-to-VA cohort for all registry complication categories, except infectious and renal (Table 3).

A summary of the ECMO durations and outcomes for all patient subgroups defined throughout the study is outlined in Table 4. A high-level

Table 3
Outcomes in neonates requiring VV-to-VA conversion compared with matched VA controls.

	VV to VA conversions ($N = 98$)	Propensity-matched isolated VA controls ($N = 364$)	P
Length of ECMO run (h)[a]	190 (122–307)	127 (94–180)	<0.001
Survived ECMO	80 (82%)	337 (93%)	0.002
Survived to discharge	69 (70%)	300 (83%)	0.01
Mechanical complications	59 (60%)	92 (25%)	<0.001
Hemorrhagic complications	32 (33%)	71 (20%)	0.009
Neurologic Complications	20 (20%)	47 (13%)	0.08
Cardiovascular complications	65 (66%)	163 (45%)	<0.001
Renal complications	29 (30%)	79 (22%)	0.11
Pulmonary complications	17 (17%)	22 (6%)	0.001
Infectious complications	4 (4%)	10 (3%)	0.51

[a] Data presented as medians with interquartile range.

comparison of outcomes between the entire isolated VV cohort and the entire isolated VA cohort (inclusive of propensity-matched cases; i.e., combining the middle two columns of Table 4 into a single group) did reveal that neonates placed on VV support had shorter ECMO runs (117 h vs. 136 h, P < 0.001), fewer neurologic complications (9.4% vs. 16%, P < 0.001), fewer hemorrhagic complications (17% vs. 23%, P < 0.001), higher ECMO survival (94% vs. 91%, P = 0.001), and higher survival to discharge rates (89% vs. 83%, P < 0.001) than those undergoing isolated VA ECMO runs. No statistical difference was detected in the mechanical complication rate between the entire VV versus VA cohort (27% vs. 26%, P = 0.63).

A second phase of investigation focused on the 1702 patients originally cannulated onto VV ECMO. When compared to neonates successfully completing an isolated VV ECMO run – similar to our findings with matched VA controls – patients requiring VV-to-VA conversion had longer median ECMO runs (190 h vs. 117 h, P < 0.001) and lower rates of ECMO survival (82% vs. 94%, P < 0.001) and survival to discharge (70% vs. 89%, P < 0.001).

The results from our initial univariate analysis comparing neonates remaining on solitary VV support versus those who required VV-to-VA conversion are summarized in Table 5. Pre-ECMO variables from Table 5 which demonstrated significant differences between standalone VV runs versus VV-to-VA conversions were subsequently entered into a stepwise logistic regression model to assess their multivariate validity in predicting conversion among neonates with MAS/PPHN. On multivariate regression, conversion was more likely if neonates on VV ECMO did not receive surfactant or required high-frequency ventilation before ECMO (Table 6).

3. Discussion

Neonatal ECMO outcomes are generally more favorable than those for older children and adults across all diagnosis categories. ELSO registry data from July 2019 demonstrate that for the preceding 5-year period, ECMO survival and survival to discharge rates for neonates with isolated respiratory failure were 83% and 68%, compared to 75% and 64% in older children and 69% and 61% in adults [1]. Our data suggest that even higher ECMO survival and survival to discharge rates – 92% and 85% – are achieved when considering only neonates with a primary diagnosis of MAS or PPHN. Clinicians consider full-term neonates with MAS/PPHN to be ideal ECMO candidates because the underlying disease is usually of short duration, reversible, and occurs against the backdrop

Table 4
Summary of key outcome variables across study groups.

		All isolated VA ECMO runs		
	Isolated VV ECMO runs ($N = 1604$)	Unmatched isolated VA ECMO runs[a] ($N = 1765$)	Propensity-matched isolated VA ECMO runs ($N = 364$)	VV to VA conversions ($N = 98$)
Length of ECMO run (h)[b]	117 (85–164)	136 (95–195)	127 (94–80)	190 (122–307)
Neurologic complications	151 (9.4%)	283 (16%)	47 (13%)	20 (20%)
Mechanical complications	430 (27%)	463 (26%)	92 (25%)	59 (60%)
Hemorrhagic complications	270 (17%)	411 (23%)	71 (20%)	32 (33%)
Survived ECMO	1503 (94%)	1593 (91%)	337 (93%)	80 (82%)
Survived to discharge	1430 (89%)	1456 (83%)	300 (83%)	69 (70%)

[a] This cohort excludes the matched VA runs, which are represented in the adjacent column.
[b] Data presented as medians with interquartile range.

of otherwise healthy organ systems [2,3]. Given that these excellent outcomes have become the national benchmark, it is critical that ECMO providers continue to assess their practice patterns to identify which clinical scenarios may negatively impact on this high standard.

VV ECMO may impart less morbidity on a neonate with MAS or PPHN compared to VA support [15,16], largely owing to carotid artery preservation and maintenance of native pulsatile cardiac output, driving many surgeons and intensivists to prefer the VV approach in hopes of a favorable outcome profile. Indeed, our Table 4 high-level overview of the larger cohorts in this dataset does reveal slightly better outcomes for VV over VA ECMO in MAS/PPHN. However, this introduces a potential pitfall, as the VV modality may not be sustainable for a variety of reasons. Progression of cardiac dysfunction and impaired systemic perfusion can complicate what initially appeared to be isolated respiratory failure. The inherent reliance of neonatal VV ECMO on a single-site, double lumen cannula ties the success of the ECMO run to the precise alignment of intake and return jets suitable for target flows [8,9,17]. Inability to optimize cannula position to maintain consistent venous return may obligate conversion from VV to VA ECMO strictly for cannula and equipment related impairments.

One notable limitation of our study was an inability to determine the actual reason for conversion from VV to VA ECMO. Additionally, the timing of conversion within the ECMO run is not reported. A decision to convert ECMO modalities is usually complex and driven by a host of factors that exceed the granularity of what is captured by ELSO registry data. These deficits in the data ultimately impact our ability to attribute pre-ECMO clinical factors and equipment-related variables directly to a conversion event, given that we cannot determine whether such conversion was driven primarily by hemodynamic deterioration (i.e., postcannulation lactate levels are not captured in the registry) versus a cannula or equipment problem. The closest proxy we could identify to suggest conversion may have been driven by a venous-drainage cannula issue is in the 35 patients who had their existing double-lumen cannula exchanged for a single-lumen venous drainage cannula during conversion; this may imply that venous drainage from the double lumen cannula had been inadequate, or was not sufficiently augmented by converting the narrow inflow lumen into another drainage lumen through a Y-connection.

Our investigation revealed that conversion from VV to VA support is a rare event (5.8% of VV runs), but when required, conveys a significant negative impact on complication rates and survival. Neurologic complications, and more specifically intracranial hemorrhage, appeared to strongly correlate with mortality in this conversion subgroup, but such complications did not appear to occur in higher numbers among those neonates who underwent exchange of their double-lumen for a single-lumen cannula. Limitations in the granularity of registry data impair our ability to discern if discontinuation of ECMO was a direct consequence of these neurologic events in conversion patients. However, just comparing the 82% ECMO survival rate in the VV-to-VA conversion cohort to the 92% ECMO survival rate of the entire study population is problematic, largely owing to the heterogeneity of the control sample and the selection biases driving decisions to initially offer VV versus VA support. These biases may similarly obscure the overall outcome differences outlined in Table 4, specifically with regard to the overall VV and VA cohorts where a broad overview of the data demonstrates higher survival and fewer complications among the entire VV subgroup compared to all VA patients. A more comprehensive analysis was therefore required to better understand the predisposing factors and consequences of having to convert from VV to VA support during a neonatal ECMO run.

Table 5
Differences in pre-ECMO and postcannulation factors for VV patients requiring conversion.

	VV to VA conversions ($N = 98$)	Isolated VV controls ($N = 1604$)	P
Pre-ECMO variables			
Female gender	42 (43%)	686 (43%)	0.99
Weight (kg)[a]	3.4 (3.1–3.9)	3.4 (3.0–3.8)	0.52
Gestational age (weeks)[a]	40 (39–41)	40 (38–40)	0.04
Age at cannulation (days)[a]	2 (1–3)	1 (1–2)	0.11
High frequency ventilation	68 (77%)	969 (65%)	0.02
Vasopressors or inotropes	55 (57%)	978 (62%)	0.33
Neuromuscular blockers	60 (62%)	932 (59%)	0.60
Systemic steroids	9 (9.3%)	248 (16%)	0.11
Inhaled nitric oxide use	87 (90%)	1455 (92%)	0.44
Surfactant administered	31 (32%)	714 (45%)	0.01
Lowest pre-ECMO pH[a]	7.21 (7.16–7.33)	7.20 (7.10–7.31)	0.15
Pre-ECMO hand-bagging	8 (8.4%)	108 (6.9%)	0.54
Pre-ECMO arrest	7 (7.1%)	95 (6.0%)	0.66
Post-ECMO variables			
Percutaneous cannulation	14 (14%)	283 (18%)	0.49
Dual-site VV cannulation	17 (17%)	282 (18%)	0.99
Avalon cannula used	10 (10%)	180 (11%)	0.87
Hollow fiber oxygenator[b]	31 / 44 (71%)	984 / 1463 (67%)	0.75
Centrifugal/nonroller pump[b]	15 / 43 (35%)	383 / 1463 (26%)	0.22
Use of hemofilter	17 (17%)	441 (28%)	0.03
ECMO flow at 4 h (L/min)[a]	0.35 (0.28–0.41)	0.35 (0.30–0.40)	0.36
ECMO flow at 24 h (L/min)[a]	0.35 (0.29–0.40)	0.35 (0.30–0.40)	0.99
Best pH at 24 h on ECMO[a]	7.36 (7.31–7.39)	7.38 (7.34–7.42)	0.01
Best pO2 at 24 h on ECMO[a]	68 (56–104)	68 (55–86)	0.18

[a] Data presented as medians with interquartile range.
[b] Reflects different denominator for cohort owing to missing data points in ELSO registry.

Table 6
Multiple logistic regression of pre-ECMO factors influencing conversion from VV to VA ECMO.

Variable	Coefficient (B)	Odds ratio	95% Confidence interval for odds ratio	*P*
Correlation (Nagelkerke R^2)	0.043	—	—	—
High-frequency ventilation[a]	0.666	1.946	1.163–3.257	0.01
No surfactant administered[a]	0.517	1.676	1.058–2.656	0.03
Gestational age (weeks)	−0.193	0.824	0.676–1.006	0.06
Age at cannulation (days)	−0.103	0.902	0.842–1.106	0.09
Systemic steroids used	0.605	1.831	0.818–4.097	0.14
Lowest pre-ECMO pH	−0.796	0.451	0.101–2.006	0.29

[a] Indicates final variables and their respective correlation measures as included in the regression model, after eliminating the remaining variables.

We began by accepting that patients who require VV versus VA ECMO most likely represent two different populations, both in illness severity and in outcome trajectories. We do, however, recognize several confounders of this assumption: (1) that some centers may not offer VV support owing to surgeon preference, local standards, or equipment limitations, resulting in more patients being cannulated for VA ECMO who might have been perfect VV candidates in the past; (2) that as shown in Table 1, there was a gradual trend towards more VA cannulations for all MAS/PPHN patients over the study period, likewise implying that perhaps lower-acuity patients are being offered VA ECMO; and (3) that in the context of ever-improving neonatal care, a trend of increasing VA utilization might imply that the overall cohort of MAS/PPHN neonates that fail conventional therapy and ultimately require ECMO is in large-part "sicker" than its counterparts were a decade ago. These caveats aside, outcome differences across VV and VA cohorts shown in Table 4 still support the general observation that neonates are likely selected for VV versus VA ECMO based on underlying disease severity.

Our null hypothesis was that VV-to-VA conversion, while inconvenient, ultimately provides the optimal support (VA) to the infant, and therefore outcomes in the conversion cohort should be similar to those in neonates placed on VA ECMO from the very beginning — that there was no inherent harm in "trying" VV ECMO. Given that the overall cohort of neonates placed initially on VA ECMO included many neonates who were so sick that VV ECMO never would have been considered, we were obligated to identify a propensity-matched subgroup that was "well-enough" to serve as a valid control against patients initially offered VV support. Of note, as can be seen in Table 4, our matched VA cohort appeared to have slightly improved outcome measures compared to the larger VA population, but these were not statistically significant (data not shown). However, despite similar outcomes to the larger VA cohort, the matched VA subgroup represented a more clinically-suitable base for comparing against the VV-to-VA conversion patients. Thus, after matching on key pre-ECMO variables, it was clear that neonates who started on VV ECMO but later required VA support did worse across virtually all outcome measures compared to matched infants on solitary VA runs. There indeed was a significant "cost" in trying VV ECMO and being forced to convert; our null hypothesis was rejected.

Having established that converting a neonate with MAS/PPHN from VV to VA ECMO was inferior to offering a clinically-matched patient VA support up-front, we next explored whether there were any factors among infants who were started on VV ECMO that could predict a higher risk for conversion. This phase of analysis required us to forgo propensity matching in the VV control group for two main reasons. Since we are trying to identify clinical parameters that might drive conversion, if we had used those same pre-ECMO clinical variables to match cohorts based on illness severity, we would have effectively eliminated the actual variances we were trying to detect. Secondly, while propensity matching the VV cohort might be useful for identifying equipment variables that impact conversion for infants who converted for cannula issues, we are unable to definitively establish the reason for conversion in this dataset and therefore cannot isolate this subgroup of conversion patients for a case-matched analysis.

We therefore proceeded with an examination of all isolated VV ECMO runs as they compared with those converting from VV to VA support, and identified a host of pre- and postcannulation parameters that held significant differences across the groups. Clinically-relevant variables from Table 5 demonstrate that VV-to-VA conversions were associated with higher rates of pre-ECMO high frequency ventilation, lower rates of surfactant administration, and lower rates of hemofiltration. Several other variables yielded statistical significance but were not clinically meaningful (i.e., best pH at 24 h of 7.36 vs. 7.38). However, when building our multiple logistic regression model to identify predictors of conversion, we only utilized precannulation variables so that the model would be clinically meaningful from the standpoint of providing guidance to a clinician choosing between VV versus VA cannulation. Multiple logistic regression confirmed that pre-ECMO high frequency ventilation and lack of surfactant administration were valid, independent predictors for converting from VV to VA ECMO. However, overall correlation strength of the model was low and given the overall heterogeneity of the study sample and retrospective nature of this analysis, it would be improper for us to draw a conclusion suggesting that all neonates with MAS/PPHN who require high frequency ventilation and did not receive surfactant be only offered VA support should they require ECMO.

A related analysis was recently performed focused solely on patients with congenital diaphragmatic hernias (CDHs) requiring ECMO [14]. The conversion rate for CDH patients from VV to VA ECMO in this study was 15%, notably higher than the 5.8% conversion rate we observed in the MAS/PPHN population; this is not surprising given the overall higher degree of illness severity in CDH patients. However, similar to our findings, VV-to-VA conversions in the CDH population were associated with higher mortality and higher rates of neurologic injury compared with solitary VA or VV ECMO runs. Another recent analysis examined a wide demographic range of ECMO patients who underwent VV to VA conversion — a 35 year study period of the ELSO registry inclusive of newborns and children through 18 years of life [18]. This analysis demonstrated increased mortality risks for neonatal and older pediatric patients, for both respiratory and cardiac diagnoses. Given the broad scope of that study, propensity matching and detailed analysis of control groups were not performed, which limited its ability to identify conversion predictors or assess clinical associations and outcome trends for specific subgroups. Against these previously-reported outcomes showing the negative impact of VV-to-VA conversion, we might have expected our study cohort to perhaps be somewhat immune to this conversion morbidity owing to the traditional association of these MAS/PPHN infants with the best ECMO outcomes. However, we demonstrated that the favorability of the MAS/PPHN cohort does not shelter them from the morbidity of VV-to-VA conversion, and this may further caution providers against undermining the precedent of excellent MAS/PPHN outcomes if they casually offer VV support in a clinical scenario where there is an elevated risk of VA conversion.

This investigation represents the only analysis of ELSO registry data to exclusively look at the impact of VV-to-VA conversion among a cohort of ECMO patients who have a highly favorable prognosis. By confining our investigation to a narrow scope of MAS/PPHN patients, we provide a more robust assessment of both the predisposing factors and outcome consequences of VV-to-VA conversion. The study's propensity matching algorithm attempts to address a common selection-bias criticism of VV versus VA comparisons by allowing us to better isolate the impact of initial ECMO modality selection, because we are able to compare infants with similar clinical pictures at the outset of their ECMO course. The analysis remains limited by its retrospective nature and dependence on the quality of the data entered, the selection bias of surgeons in choosing the initial mode of either VV or VA support, and granularity of clinical variables available in the ELSO registry. As mentioned above, we are additionally constrained by the absence of data that can allow us to identify the proximate reasons for conversion, as this limits our ability to differentiate conversions driven by hemodynamics versus equipment. Assuredly there are additional confounding variables not captured by the registry which could impact our findings, and likely could only be addressed through expansion of registry variables or more ideally through large, multicenter prospective observational studies.

The demonstration of increased morbidity and mortality of VV-to-VA conversion from this study and other recent investigations takes on added significance owing to recent events affecting the national availability of double lumen VV cannulae for neonates [19]. With few programs willing to take on the added risks of placing a bicaval Avalon® cannula into a neonate [17,20], ECMO providers may need to further restrict which neonates can be offered VV support based on equipment availability. Our data outlined in Table 1 do begin to hint at a trend towards decreasing VV-to-VA conversions

over the past several years, though there are insufficient data points to determine whether this is normal variation versus a true signal. However, if future registry data affirm this trend in fewer conversions, it might indeed reflect more selectivity in choosing appropriate VV candidates, driven either by growing awareness of the inferior outcomes associated with conversion, or out of necessity owing to supply-chain limitations. Faced with these dilemmas, our data may help providers identify patients at higher risk for conversion and allow them to consider the consequences of converting a patient versus offering them up-front VA support.

4. Conclusions

These findings corroborate previous reports that conversion from VV to VA ECMO carries increased morbidity and mortality compared to those initially offered VA ECMO, with focus specifically on neonates with MAS/PPHN. The analysis argues against the idea that it is always worth "trying" VV ECMO for borderline cases, given that conversion from VV to VA support imparts clearly inferior outcomes. Data from this study should reassure providers that offering a neonate with MAS/PPHN up-front VA ECMO is a reasonable option, and is a trend that appears to be increasing over time. If current supply-chain obstacles continue to limit the availability of double-lumen VV cannulae, providers can consider leveraging these findings for a subset of MAS/PPHN infants who have not received surfactant and who require high frequency ventilation as a cohort that could be offered VV ECMO in a more selective fashion.

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