Inotrope Needs in Neonates Requiring Extracorporeal Membrane Oxygenation for Respiratory Failure

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Objective To evaluate how inotropic requirements in neonates with respiratory failure are affected by extracorporeal membrane oxygenation (ECMO) mode and whether high requirements predict mortality.

Study design This retrospective chart review included all neonates undergoing ECMO for primary respiratory failure from 2010 to 2016 at a single institution. The vasoactive inotropy score (VIS) was calculated as described in the literature. Data were analyzed with descriptive statistics and univariate analyses.

Results Of the 110 identified neonates, 96 underwent venovenous (VV) (87%), 11 (10%) venoarterial, and 3 (3%) converted from VV to venoarterial. The median precannulation VIS score was 33.02 for patients who underwent VV compared with 28.93 for venoarterial ($P = .25$) and 15 for infants converted. VIS decreased dramatically by 4 hours of ECMO in both groups. The VIS before cannulation was similar in survivors and nonsurvivors, but was significantly higher in nonsurvivors after 24 hours of ECMO (median VIS, 12 [IQR, 8-25] vs 8 [IQR, 3.0-14.5]; $P = .035$) and at decannulation (10 [IQR, 7-19] vs 3 [IQR, 0-7]; $P < .001$).

Conclusions Neonates with respiratory failure can be successfully managed on VV ECMO even with considerable vasoactive requirements. Vasoactive requirement after 24 hours of ECMO was predictive of mortality. *(J Pediatr 2019;214:128-33)*.

Extracorporeal membrane oxygenation (ECMO) was first successfully used in a newborn in 1976 by Dr Robert Bartlett.[1,2] Although the indications for use and disease processes have changed over time, ECMO continues to be a life-saving technology for select infants with respiratory and cardiorespiratory failure. Both venovenous (VV) and venoarterial (VA) ECMO are used successfully and have different advantages. Potential benefits of VV ECMO include sparing of the carotid artery, myocardial perfusion with oxygenated blood, pulsatile blood flow, and potential emboli directed towards pulmonary rather than systemic circulation.[1,2] However, only VA ECMO provides direct cardiac and blood pressure support. VA ECMO is used more frequently in neonatal respiratory patients, despite historical data demonstrating an association with increased mortality and neurologic sequelae.[3-7]

Several centers have shown that use of VV ECMO as the primary approach for neonates with respiratory failure has good outcomes.[8,9] Despite the advantages of VV ECMO, the use of VV ECMO for neonatal respiratory failure has not increased over time, unlike the trends seen in pediatric and adult ECMO patients.[10,11] According to the Extracorporeal Life Support Organization registry, only 27% of ECMO runs for neonatal respiratory failure in 2017 were VV.[12] Common reasons for choosing VA ECMO include the severity of hypotension and the degree of inotropic support needed, as well as ventricular dysfunction on echocardiogram.[13] It remains unclear if increased mortality and morbidities in VA ECMO patients are due to inherent differences between ECMO modes or if outcomes are confounded by the hypotension and ventricular dysfunction that are commonly cited as indications for VA ECMO.[13]

A vasoactive inotropic score (VIS) has been described as a means of quantifying the amount of cardiovascular support an infant requires and as a marker for disease severity.[14,15] In cardiac patients, a high VIS has been associated with increased mortality, prolonged cardiac intensive care unit stay, duration of mechanical ventilation, and time to negative fluid balance.[14-16] A high VIS has also been associated with intensive care unit length of stay, ventilator days, mortality, and a composite outcome of cardiac arrest, ECMO, and in-hospital mortality in pediatric sepsis.[17,18] To date, there are no published

CDH	Congenital diaphragmatic hernia
ECMO	Extracorporeal membrane oxygenation
+V	Additional venous drain
VA	Venoarterial
VIS	Vasoactive inotropic score
VV	Venovenous

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Table I. Study population characteristics

Patient variables	VV ECMO (n = 96)	VA ECMO (n = 14)	*P* value
Gestational age (weeks)	39 (38, 39.5)	37.5 (36, 39)	.05
Birth weight (kg)	3.20 (2.80, 3.61)	3.38 (2.51, 3.49)	.66
Race			.52
Caucasian	4 (29)	39 (41)	
Black	46 (48)	9 (64)	
Other	11 (11)	1 (7)	
Female sex	38 (40)	5 (35)	.78
DOL at time of cannulation (days)	1 (1, 2)	1 (1, 5)	.42
Last pH before ECMO	7.27 (7.16, 7.35)	7.30 (7.28, 7.38)	.08
Worst pH before ECMO	7.19 (7.07, 7.26)	7.17 (7.09, 7.23)	.52
5-min APGAR	7 [5-8]	7.5 [5-8]	.52
Oxygenation index before ECMO	45.0 (33.5, 65.0)	55.0 (39.0, 67.0)	.22
Primary diagnosis			.07
CDH	37 (39)	6 (43)	
Meconium aspiration	31 (32)	1 (7)	
Sepsis/pneumonia	3 (3)	2 (14)	
Idiopathic pulmonary hypertension	23 (24)	4 (29)	
Other	2 (2)	1 (7)	
Total days on ECMO (days)	6 (5, 11)	8.5 (7, 11)	.06
Survival off ECMO	79 (82)	10 (71)	.47
Survival to discharge	70 (73)	9 (64)	.53
Survival to discharge without severe brain injury	67 (70)	8 (57)	.37
ECMO complications			
Arrhythmias	4 (4)	0	>.999
Hypertension	1 (1)	0	>.999
CNS bleed	12 (13)	1 (7)	>.999
CNS infarction	1 (1)	1 (7)	.24
Seizures (clinical)	1 (1)	2 (14)	.0422
Mechanical: clot	6 (6)	4 (29)	.0226

CNS, central nervous system; *DOL*, day of life.
Values are median (25th, 75th), median [range], or number (%). The *P* values were calculated using the Wilcoxon rank-sum tests and χ^2 tests (or Fisher exact tests for cell counts <5).

studies evaluating the use of VIS in neonates with cardiorespiratory failure who were treated with ECMO.

The objectives of this study are to demonstrate that neonates with high inotropy needs can be successfully managed with VV ECMO and to evaluate the ability of VIS to predict mortality in neonates requiring ECMO.

Methods

This retrospective chart review used the Children's Healthcare of Atlanta at Egleston ECMO database and electric medical record. The database identified neonates requiring ECMO for respiratory failure in the neonatal intensive care unit between January 1, 2010, and December 1, 2016. ECMO is offered to neonates at our institution who meet the institutional inclusion and exclusion criteria as previously published.[8] The institutional review board at our hospital approved this study.

Vasoactive and inotropic drip dosages were obtained from the medical record. The maximum VIS was calculated as previously described: dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + (100 × epinephrine dose [μg/kg/min]) + (10 × milrinone dose [μg/kg/min]) + (10 000 × vasopressin dose [U/kg/min]) + (100 × norepinephrine dose [μg/kg/min]).[15] The VIS was calculated before cannulation (as recorded within <1 hour of ECMO start), at 4 hours on ECMO, 24 hours on ECMO, and before decannulation. Echocardiogram results were taken from the official echocardiogram report.

A roller head pump is used for ECMO support in the Children's Healthcare of Atlanta at Egleston neonatal intensive care unit. Our institutional preference is to support all patients with VV ECMO using 13F or 16F Origen cannulas (Origen Biomedical, Austin, Texas) with the additional use of a cephalad cannula if vessel size allows (additional venous drain [+V]). The indication for VA ECMO initiation or conversion was collected. Primary infants with VA and infants converted from VV to VA were classified in the VA group for data analysis.

Statistical Analyses

Descriptive data were presented as medians with 25th and 75th percentiles for continuous data or counts and percentages for categorical data. Comparisons were done using Wilcoxon rank-sum tests for continuous variables or χ^2 or Fisher exact tests (if cell counts were <5) for categorical variables. Cochran-Armitage trend tests were used to test for increasing or decreasing trends in the percentage of those who survived to discharge across increasing VIS quartiles. All statistical analysis was performed using SAS 9.4 (SAS, Cary, North Carolina) and statistical significance was assessed at the .05 level.

Results

A total of 110 neonates met the inclusion criteria for the study: 96 VV+V (87%), 11 (10%) VA+V, and 3 (3%) converted from VV+V to VA+V. Indications for VA+V ECMO

included the inability to place VV cannula (n = 10) and outflow obstruction (n = 1). Conversions to VA ECMO occurred secondary to VV cannula kinking (n = 1) and persistent hypoxia (n = 2). Characteristics of the study population are shown in Table I. Patients with VA were slightly younger and there was a trend toward longer runs; otherwise, the groups were similar. Survivors and nonsurvivors differed with respect to a higher frequency of congenital diaphragmatic hernia (CDH) diagnosis (68% vs 28%, $P = .001$) and longer ECMO runs in nonsurvivors (11 days [IQR, 6-15 days] vs 6 days [IQR, 5-8 days]; $P < .001$). Survival varied by primary diagnosis and was the highest for meconium aspiration (93.8%), lowest for CDH (51%), and intermediate for other diagnoses (pneumonia 60%; idiopathic pulmonary hypertension 81.5%).

A comparison of complications between ECMO modes found a higher incidence of clinical seizures and circuit clots in the VA group, but not central nervous system hemorrhage or infarction. Complications were also more common in nonsurvivors (data not shown). Despite all but 2 patients receiving inotropic medications, the majority had preserved cardiac function, with right or left ventricular dysfunction reported on echocardiogram in 37 and 10 patients, respectively, indicating that the bulk of inotropic use was for blood pressure support alone.

The median VIS precannulation, 4 hours after cannulation, 24 hours after cannulation, and decannulation can be seen in Figure 1, A and B. The VIS at 24 hours was not available for 3 patients (2 VV+V, 1 VA+V) because ECMO had been discontinued owing to intracranial hemorrhage. The VIS declined in a similar fashion over time regardless of ECMO mode, with a marked decrease within the first few hours of initiating ECMO. There were no statistically significant differences in the VIS at any time point between VV and VA ECMO groups. In general, VIS precannulation was poorly predictive of survival to discharge (Table II). We did find the highest quartile with a VIS of >40 had a trend toward higher mortality (Figure 2). The VIS at 24 hours of ECMO and at decannulation were both predictive of survival (Figure 1, B and Table II). For every 5-point increase in the VIS at 24 hours of ECMO, the probability of survival decreased by 8%.

Discussion

Neonates who require ECMO are some of the most critically ill patients cared for in the neonatal intensive care unit and have high mortality and morbidity rates attributed to both illness and ECMO therapy. With changes in the neonatal ECMO population, poor outcomes are increasing rather than decreasing over time.[4,10] Based on available data, VV ECMO offers the potential of improved neurologic outcomes over VA ECMO, although high inotropy needs are often a reason patients are not considered candidates for VV ECMO.[13] The VIS has been used in pediatric and cardiac populations to quantify the amount of cardiac pharmacologic support required and found to predict outcomes,[14-18] but its use has not been described in neonatal ECMO. In this study, we used VIS as a proxy to show that infants with high inotropy requirements can be supported with VV+V ECMO. Additionally, we evaluated the potential for VIS to be a predictor of survival at different time intervals on ECMO.

The debate about the best ECMO mode is longstanding, and preferences continue to vary by center with an overall preference for VA ECMO in neonatal respiratory failure.[5,10,19-21] The evidence that patients treated with VV ECMO have higher survival rates and fewer neurologic sequelae is consistent across multiple studies.[7,22] However, there are no randomized trial data available, and any comparison is limited by the fact that smaller, sicker patients with greater inotropy needs are frequently preferentially placed on VA ECMO. In our population, the patients treated with VA were younger with a higher proportion of CDH, both of which affect outcomes.[11,21,23] One analysis of patients with CDH matched for level of illness showed equal survival, but fewer neurologic sequelae in those treated with VV ECMO.[5] We previously showed a decrease in neurologic morbidities in neonatal respiratory patients on ECMO treated primarily with VV+V ECMO compared with the Extracorporeal Life Support Organization database as a whole.[8]

In this study, we found a dramatic decrease in inotropy needs in the first hours of ECMO regardless of mode. One of the benefits of VA ECMO is providing direct blood pressure support by delivering blood flow directly into the arterial system, and certainly in patients with primary cardiac disease this component is essential.[1,2] Either ECMO mode offers correction of hypoxia and acidosis, which can have substantial impact on inotropy needs. VV ECMO also provides oxygenated blood to the myocardium, potentially maintaining or recovering native cardiac function.

These data suggest that the degree of inotropy requirement should not dictate a need for VA ECMO. There were no significant differences in VIS between the VA and VV groups at any time point, and neonates in both groups initially had high inotropy needs. The variation between VIS at cannulation in the VA vs VV nonsurvivors likely resulted from the small study numbers[4] rather than a true difference. Indications for VA ECMO cannulation were heterogenous owing to the inclusion of patients originally cannulated on VA ECMO and patients converted from VV to VA ECMO, which further limited our ability to directly compare the groups. Because historical data demonstrate greater mortality and morbidity in VA ECMO, we suggest our data should encourage consideration of VV ECMO, even for neonatal respiratory failure with high inotropy needs.

The VIS does correlate with outcomes in pediatric intensive care and postoperative cardiac populations but, until now, it has not been evaluated in the neonatal ECMO population. In infants who had undergone cardiac surgery, Gaies et al showed that a high VIS in the first 24 hours was

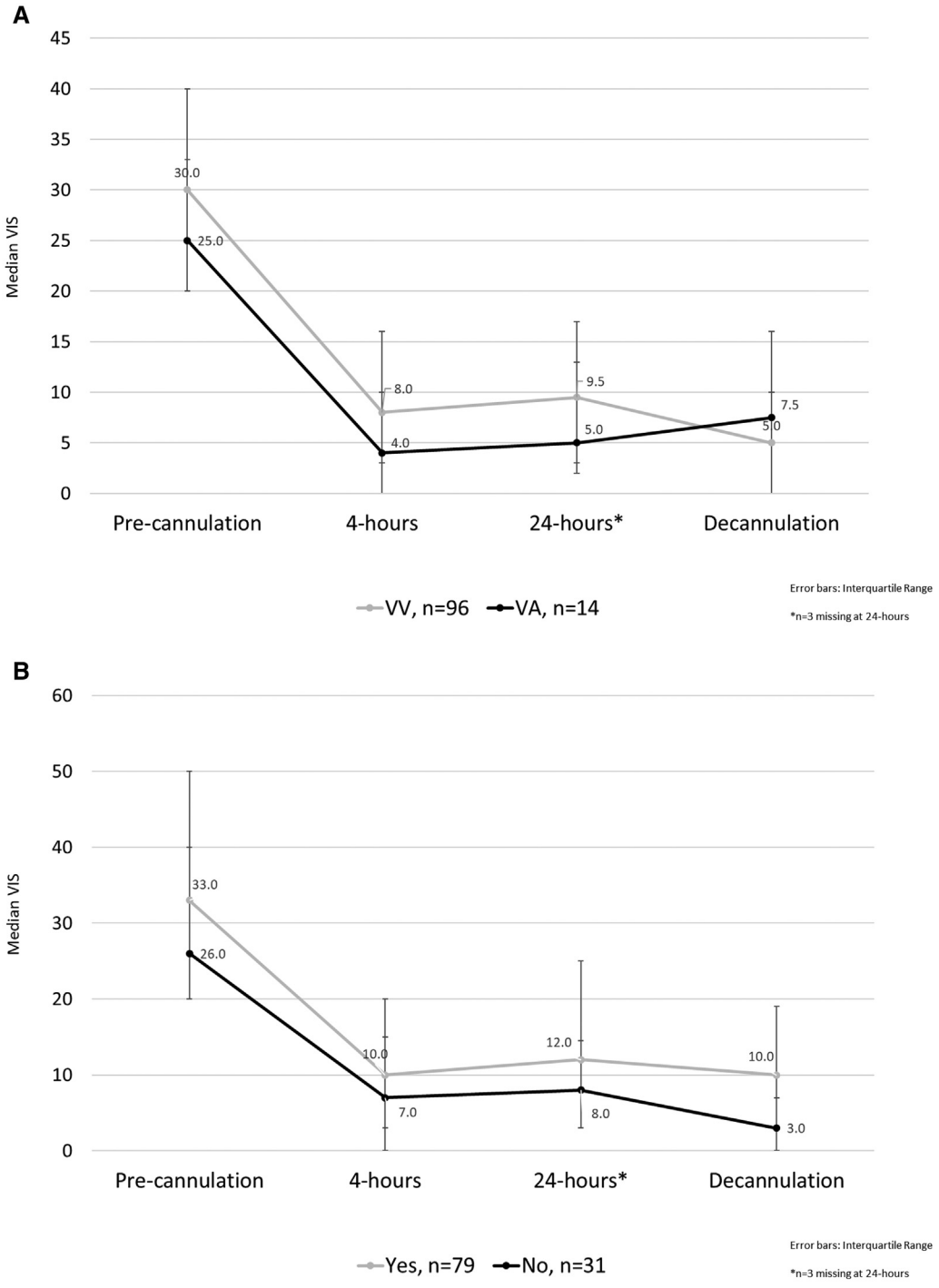

Figure 1. **A,** Median VIS over time compared by ECMO mode, venovenous (*gray*) or venoarterial (*black*). Error bars represent interquartile range. **B,** Median VIS over time in survivors (*gray*) and nonsurvivors (*black*). Error bars represent interquartile range.

predictive of both mortality and morbidities, including prolonged intubation and longer length of stay.[14,15] VIS has also been evaluated in pediatric patients with septic shock; a VIS of >20 in the first 48 hours was associated with increased mortality and, when evaluated over time, the VIS at 48 hours was the most predictive of outcome.[17,18]

In our cohort, the precannulation VIS was not predictive of mortality, except for a trend in the patients in the highest quartile. Perhaps this is due to the inherent characteristics of our neonatal ECMO population, where both high inotropy and mortality were common. In fact when stratified by mode, a lower VIS was predictive of death in the VA group, a finding we attributed to small sample size because it was not consistent across time points.

The association of VIS at decannulation with survival was anticipated; a higher VIS likely correlates clinically with

Table II. VIS as a predictor of survival to discharge

Patient variables	Total	Survived to discharge (n = 79)	Did not survive to discharge (n = 31)	*P* value
VIS at precannulation				
Total	30 (20, 40)	26 (20, 40)	33 (20, 50)	.23
VV	30 (20, 40)	26 (20, 40)	37.5 (28.0, 50.0)	.0211
VA	25 (20, 33)	30 (25, 35)	15 (10, 20)	.0228
VIS at 4 hours				
Total	8 (3, 15)	7 (3, 15)	10 (0, 20)	.30
VV	8 (3, 16)	7 (3, 15)	12.75 (3.00, 20.00)	.16
VA	4 (0, 10)	7 (0, 10)	3 (0, 5)	.098
VIS at 24 hours				
Total	9 (3, 16)	8.0 (3.0, 14.5)	12 (8, 25)	.0347
VV	9.5 (3, 17)	8.0 (3.0, 14.5)	13.5 (8.0, 25.0)	.0127
VA	5 (2, 13)	7.5 (3.5, 14.0)	5 (2, 11)	.71
VIS at decannulation				
Total	5 (0, 10)	3 (0, 7)	10 (7, 19)	<.0001
VV	5 (0, 10)	3 (0, 7)	10 (7.5, 17.5)	<.0001
VA	7.5 (0, 16.0)	5 (0, 13.0)	18 (5, 20)	.18

Data are median (25th, 75th) or number (%). The *P* values were calculated via the Wilcoxon rank-sum test comparing VIS scores by survival status. $P < .05$ was considered significant.

patients with complications who require abrupt discontinuation of ECMO support, often with high inotropic needs. Interestingly, a lower VIS score at 24 hours did seem to predict survival in our population, perhaps demonstrating response to therapy and providing a clinically useful gauge. In our center, conversion from VV to VA ECMO is typically performed for signs of continued poor end-organ perfusion after ECMO has commenced, such as hypoxia or acidosis, and not for continued inotropic needs alone. It is possible that earlier conversion or initial selection to VA could have changed the outcome for patients with a higher VIS at 24 hours, but this hypothesis would need to be validated in larger studies across multiple ECMO centers to include more VA and converted patients.

There are limitations to our study. This was a retrospective study at a single institution with specific practice patterns. Inotropic drug use can be both subjective and variable and, with no standard indication for specific vasoactive medications or dosages, differences exist in medication selection, blood pressure goals, and dosing ranges among centers, diseases, and individual practitioners. Without standardization, different preferences in the choice of inotropic drugs can alter the VIS score, making it challenging to extrapolate results in a multicenter cohort. For example, our institution is a relatively high user of milrinone, which is a component of the continued inotropy use recorded at decannulation in 64% of our patients (70/110) thus affecting the VIS score. Perhaps the largest limitation in our study is our center's preferential use of VV ECMO. This practice biases the patient selection to the VV group with fewer patients in the VA group, limiting the ability to analyze the difference between the two groups and the external validity of our findings. In addition, both hypotension and ventricular dysfunction contribute to inotropic medication use, but we focused here on inotropic treatment alone and did not explore the presence or absence of cardiac dysfunction on outcome, although that remains a central consideration in the selection of ECMO mode and impact on the choice of medications. Despite these weaknesses, we believe the results demonstrate that patients with significant inotropy needs can be successfully supported by VV+V ECMO.

In conclusion, neonates with respiratory failure can be successfully managed on VV ECMO, even with considerable vasoactive requirements. Given the potentially decreased morbidity associated with VV ECMO, we recommend

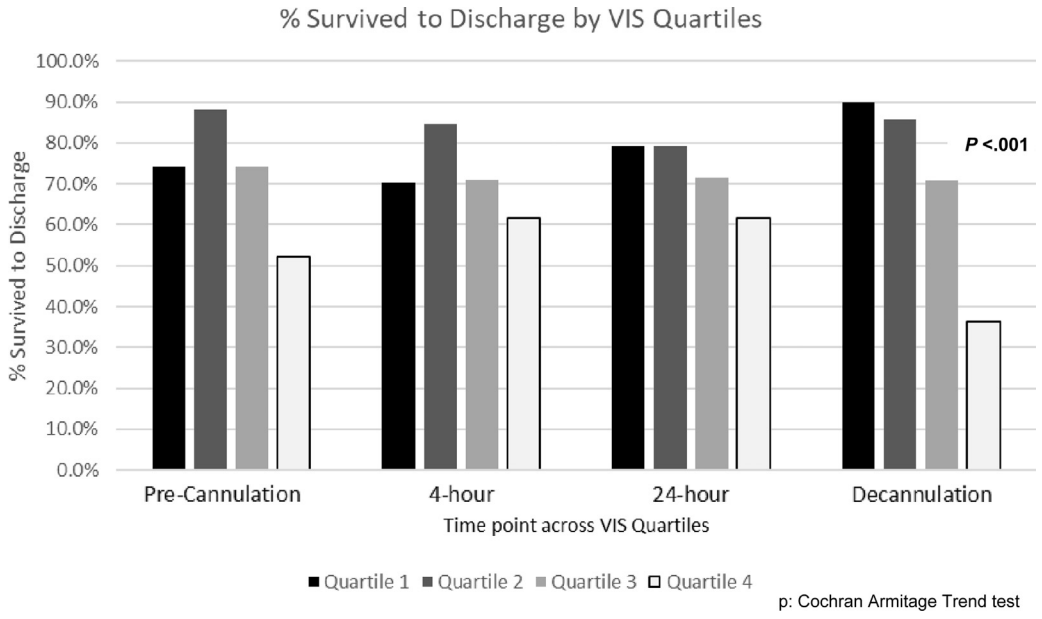

Figure 2. Percentage of patients surviving to discharge by vasoactive inotrope score VIS quartile at each time-period. $P < .001$ for the highest quartile at decannulation.

consideration of VV ECMO initially. VIS before treatment was minimally predictive of outcome; however, continued inotropic requirements after 24 hours of ECMO therapy predicted mortality in neonates with respiratory failure. This finding might be useful to physicians when counseling families and making clinical management decisions. Future studies are needed to validate our observations across centers with higher VA ECMO use, ideally with standardized analysis of echocardiograms and inotropic medication administration. ■

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