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Original Article

Disruption of Cerebral Autoregulation Prior to Extracorporeal Membrane Oxygenation Cannulation Contributes to Neurologic Injury in Pediatric Patients

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ABSTRACT

Aim: Neurologic complications are a significant cause of morbidity and mortality for children supported with extracorporeal membrane oxygenation (ECMO). Disruption of cerebral autoregulation (CAR) is associated with neurologic injury for children who require ECMO. The aim of this project was to identify the period of ECMO support which carries the greatest risk of neurologic injury.

Materials and Methods: This retrospective cohort study was conducted in children supported on venovenous or venoarterial ECMO between 2020 and 2023 at a single quaternary center. CAR was measured by assessing the wavelet transform coherence of mean arterial blood pressure and cerebral oximetry. Disruption of CAR was assessed by the time-period of ECMO support and then compared between patients in order to determine the association between impaired CAR and neurologic injury determined by neuroimaging.

Results: A total of 31 neonates and children who received ECMO support were included. Eleven children developed severe neurologic injury (35%). Peak disruption of CAR during the pre-cannulation period correlated with severe neurologic injury (R^2=0.14, p=0.04). Peak disruptions of CAR in the peri-cannulation (R^2=0.004, p=0.7) and post-cannulation periods (R^2=0.04, p=0.28) were not significant. There were no significant differences in laboratory values or anticoagulation between the groups. There were no differences in CAR disruption between the neonates and the children [18.4 (8.6-35) p=0.09] or for extracorporeal cardiopulmonary resuscitation with respect to the other indications for ECMO [17.5 (6.5-35), p=0.5].

Conclusion: Impaired CAR in the 24 hours preceding ECMO support may represent the most critical window for neuroprotection in pediatric ECMO.

Keywords: Extracorporeal membrane oxygenation, neurologic injury, pediatrics, cerebral autoregulation

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Introduction

Extracorporeal membrane oxygenation (ECMO) is a form of cardiopulmonary bypass which provides temporary support to critically ill children whose illness is progressing despite maximal conventional therapies. Advances in ECMO have allowed more children to survive an otherwise fatal illness. However, neurologic injury remains a significant cause of morbidity and mortality. Even with the best care, 15-35% of patients surviving ECMO experience significant neurologic injury (1-7).

The risk factors for neurologic injury are varied and multifactorial. Recent work has identified an association between disruptions in cerebral autoregulation (CAR) and neurologic injury for patients on ECMO (8-10). In a healthy child, the brain maintains stable blood flow over a wide range of blood pressures through a physiologic control system known as CAR. Multiple factors of critical illnesses such as hypoxemia, hypercarbia, and acidemia can cause disruptions in CAR (11,12). Intra-ECMO factors including rapid corrections of CO_2 (13,14), mechanical stress on major blood vessels, and alterations of pulsatile flow patterns also play a role in altered CAR (15,16). The period of ECMO support which confers the greatest risk for neurologic injury is currently unknown.

In this study, we sought to identify the period of ECMO support which confers the greatest burden of impaired CAR and, thus, the risk of the development of neurologic injury. As patients experience rapid changes in physiologic factors during the peri-cannulation period, we hypothesize that this will lead to the greatest disruption of CAR and more severe neurologic injury.

Materials and Methods

Participants

This retrospective cohort study included neonatal and pediatric patients (0 to 18 years) who were supported on ECMO from August 2020 to December 2023 at the Children's Medical Center, Dallas. With University of Texas Southwestern Medical Center Institutional Review Board approval (approval number: STU-2023-0788, date: 28.08.2023), electronic medical record data was extracted for eligible patients. Those patients who had previously received ECMO support or did not have neurologic imaging within 30 days of decannulation were excluded from this study. Those patients who did not have near-infrared spectroscopy (NIRS) data or blood pressure data for the 4 hours prior to cannulation through to 72 hours after cannulation were excluded from the analysis. The reasons for ECMO intervention were varied and consisted of persistent pulmonary hypertension of the newborn (PPHN), cardiogenic shock, extracorporeal cardiopulmonary resuscitation (eCPR), septic shock and acute respiratory distress syndrome (ARDS). All patients were cared for in the pediatric or cardiac intensive care unit. Clinical management was under the purview of the patient's primary intensivist and followed institutional guidelines. Cannulation was performed by the general and cardiovascular surgical teams.

Data Collection

Patient demographics, ECMO factors and laboratory data were obtained from the electronic medical records. All patients received continuous hemodynamic monitoring which included mean arterial pressure measured through an indwelling arterial catheter. Cerebral tissue oxygen saturation (rSO_2) was measured on the forehead using Near Infrared Spectroscopy (17-21). Both signals were sampled every 5 seconds and recorded throughout the ECMO run, except during patient transportation for imaging or other procedures. Laboratory testing pre- and during ECMO followed institutional standards. For this study, the extracted data included bilirubin, blood gas parameters (pH, pO_2, and pCO_2), lactate, platelet, fibrinogen, hemoglobin, plasma-free hemoglobin, and daily mean anticoagulant dose.

Neuroimaging Assessment and Scoring

It is standard care at our institution that post-ECMO magnetic resonance imaging (MRI) is obtained within 30 days of decannulation. If there is concern of an acute change in neurologic status during the ECMO run, an emergent computed tomography (CT) is often obtained. Intra- and post-ECMO neuroimaging of the recruited subjects were scored using a previously validated categorical scale (22,23) which is predictive of functional neurodevelopmental outcome (10,24). The neuroradiologists who carried out the scoring were blinded to the clinical course and study findings. This scoring system divided intracranial injuries into three categories: hemorrhagic, ischemic and ventricular dilation. Injuries were assigned numeric scores based on their severity and weighted with an a priori assumption of the risk of neurologic sequelae. In the case that a patient had both intra-ECMO CT and post-ECMO MRI, the CT imaging was analyzed for scoring purposes. Neuroimaging scores were grouped into two categories: no/minimal injury (score 0 to 8) or severe injury (≥9). A cut-off score of ≥9 was selected as prior work had demonstrated this correlates with unfavorable neurocognitive outcomes in pediatric patients (24).

Autoregulation Measurement

Wavelet transform coherence (WTC) is an advanced data analysis tool in the time-frequency domain for studying non-stationary time series and the relationship between two synchronous time series. WTC has been used to assess CAR by calculating the coherence metrics between mean arterial blood pressure (MAP) and cerebral oximetry (rSO_2 from NIRS) (10,25-27). In principle, WTC provides two key parameters: (1) cross-wavelet coherence magnitudes between the two signals across time and frequency, and (2) phase information between the two signals, indicating whether they are in phase (moving together), anti-phase (moving in opposite directions), or lead-lag relationships. As a WTC approach utilizes nonstationary signals and analyzes signals across time and frequency, it is better at assessing the dynamic changes in CAR compared to other methodologies (27). These WTC results are typically visualized as a color-coded time-frequency plot (known as a scalogram), where coherence values range from 0 (no correlation) to 1 (strong correlation), and arrows indicate the phase relationship between the two signals. In this study, 0 represents the lowest impaired CAR burden and 1 represents complete coherence of the wavelets, i.e., the highest disrupted CAR burden. In this study, we focused on the pressure-passive state which signifies impaired autoregulation and leads to high in-phase coherence between MAP and rSO_2 fluctuations (27).

In addition, this study followed a new analysis strategy in order to quantify time-resolved percentage time of significant coherence (trSC in %) (27). Yu et al. al. (27) provides a narrative explanation of a WTC computational package using a graphical flowchart for clinicians, and it also introduces a novel method which allows quantification of temporal changes in trSC (%) in order to examine CAR impairment during the pre-, peri-, and post-cannulation periods in the selected patient population. Specifically, a temporal window, such as 30 or 60 min (1 h), was chosen in a pre-selected frequency or scale range [scale=1/(Morlet-wavelet frequency)] within the time-frequency WTC scalogram. Then, the averaged percentage time of the significant coherence (across both time- and scale-ranges) was obtained for each temporal window to form time-dependent WTC indices as CAR burden (27).

Peak and averaged autoregulation disruption were calculated for each patient in three time periods: pre-cannulation (-24 h to 0 h), peri-cannulation (0 h to +12 h) and post-cannulation (+12 h to +72 h); where hour zero denotes the time of cannulation. Peak and median autoregulation disruption was then compared for the injury group vs no/minimal injury group.

Statistical Analysis

Demographics, ECMO factors, laboratory parameters and outcomes were compared for patients in the injury and no/minimal injury groups. Continuous variables were analyzed with Student's t-test if normally distributed or Wilcoxon-Mann-Whitney univariate analysis for non-normally distributed variables and are expressed as median with 25th-75th interquartile ranges. Regression analysis was performed in order to evaluate the relationship between autoregulation disruption and neuroimaging scores. A p value of <0.05 was considered statistically significant.

Results

A total of 153 neonates and children received ECMO during the study period. As shown in Figure 1, patients were excluded if they did not receive neuroimaging within 30 days of decannulation or if cerebral oximetry data was missing for any of the study time periods. Thirty-one patients were included in the final analysis.

The predominant diagnosis in the neonates was PPHN, and in the children, it was eCPR followed by ARDS. The predominant ECMO type was venoarterial (VA) (n=25, 81%). As shown in Table I, 11 patients (35%) had severe neurologic injury, with similar incidence in the children and the neonates. All severe injuries were observed in those patients supported on VA ECMO and the predominant indication for ECMO in the injury group was eCPR. There were no significant differences in the laboratory values between the groups. All patients received a loading dose of heparin prior to cannulation and daily mean heparin doses were similar between the groups. Survival was similar between the groups with 85% of patients surviving to hospital discharge in the no/minimal injury group and 72% surviving to hospital discharge in the severe injury group.

Autoregulation disruption was calculated in peaks and averages for the no/minimal injury and severe injury groups. As shown in Table II, this was further stratified into the pre-cannulation period (-24 h to 0 h), the peri-cannulation period (0 h to 12 h) and the post-cannulation period (+12-72 h). It should be noted that the pre-cannulation time period varied between -4 h and -24 h. There were no significant differences when comparing the averages of disrupted autoregulation between the time periods and the development of neurologic injury (pre-cannulation: $R^2=0.07$, $p=0.15$, peri-cannulation: $R^2=0.02$, $p=0.43$, post-cannulation: $R^2=0.08$, $p=0.12$). However, there was a statistically significant correlation between peak autoregulation disruption in the pre-cannulation period and development of neurologic injury for those with severe injury ($R^2=0.14$, $p=0.04$) (Figure 2). As seen in Table III, there were no significant differences in peak CAR disruption between neonates versus children ($p=0.09$) or between eCPR versus other indications ($p=0.32$).

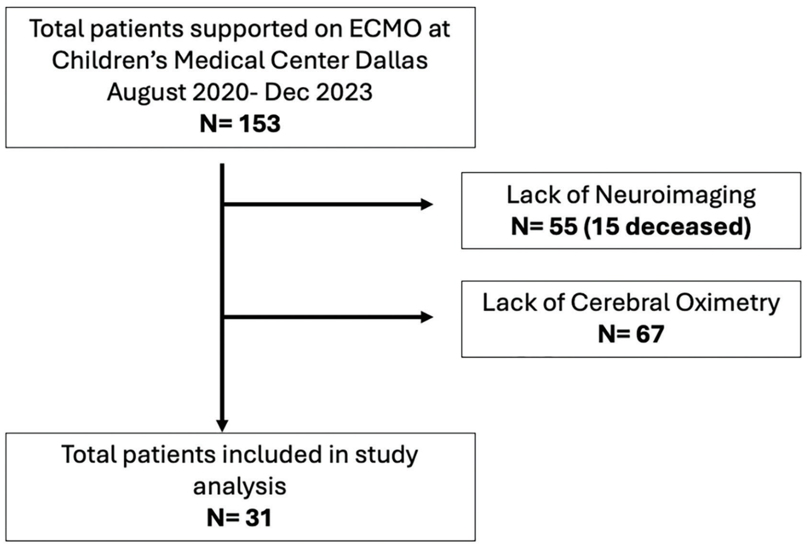

Figure 1. Flowchart of patient identification, inclusion and exclusion. Patients were excluded if neuroimaging was not completed within 30 days of decannulation. Fifteen patients died prior to obtaining neuroimaging. Sixty-seven patients did not have cerebral oximetry values for all periods of ECMO support and therefore were removed from the study analysis
ECMO: Extracorporeal membrane oxygenation

Table I. Admission characteristics, ECMO factors, laboratory parameters of the study cohort (n=31)

Patient group, n	No injury, n=20	Severe injury, n=11
Age groups		
Neonates n=12	35% (7)	45% (5)
Children n=19	65% (13)	55% (6)
Gender		
Male n=19	55% (11)	73% (8)
Female n=12	45% (9)	27% (3)
Primary diagnosis		
PPHN n=4	10% (2)	18% (2)
Septic shock n=4	10% (2)	18% (2)
ARDS n=7	35% (7)	0
eCPR n=9	20% (4)	45% (5)
Cardiac n=7	25% (5)	18% (2)
Type of ECMO		
VV n=6	30% (6)	0
VA n=25	70% (14)	100% (11)
Worst laboratory values prior to ECMO cannulation, median (25%-75% interquartile range)		
Highest bilirubin (mg/dL)	0.9 (0.4-6.6)	1.4 (0.75-3)
Lowest pH	7.15 (7.1-7.20)	7.18 (7.1-7.22)
Lowest PaO_2 (mmHg)	53.5 (37.5-70)	65 (51.5-107.5)
Highest pCO_2 (mmHg)	66.5 (58.75-102.3)	56 (51.5-75.5)
Highest lactate (mmol/L)	4.15 (1.9-6.8)	8.3 (4.85-14.5)

Table I. Continued						
Patient group, n	**No injury, n=20**			**Severe injury, n=11**		
Maximum changes of arterial blood gas from pre-ECMO to 24 h on ECMO, median (25%-75% interquartile range)						
Increase in pH	0.24 (0.19-0.28)			0.18 (0.155-0.28)		
Increase in pO_2 (mmHg)	164 (34.75-299)			94 (63.5-115.5)		
Decrease in pCO_2 (mmHg)	24.5 (17.25-47.8)			17 (13.5-38)		
Decrease in lactate (mmol/L)	2.05 (0.89-3.99)			5 (2.3-10)		
Intra-ECMO laboratory values, median (25%-75% interquartile range)						
	Day 1	**Day 2**	**Day 3**	**Day 1**	**Day 2**	**Day 3**
Hb (g/dL)	9.55 (87.7-10.4)	10 (9.5-10.8)	9.9 (9.3- 10.5)	9.4 (8.65-9.8)	9.5 (8.9-10.45)	9.2 (8.75-10.6)
Daily lowest platelet (thousand/mm^3)	92.5 (64-142)	88 (78-113)	80 (72-126)	79 (48.5-110)	85 (67.5-108.5)	80 (63.5-109)
Daily lowest fibrinogen (mg/dL)	164 (150-241)	230 (152-302)	298 (180-376)	144 (123.5-177)	235 (160-270)	284 (227-327)
Daily highest plasma free Hb (mg/dL)	35 (30-55)	50 (40-85)	60 (50-80)	70 (70-110)	85 (37.5-135)	50 (40-60)
PTT	88 (59.3-107)	102 (78.8-154)	86.5 (74-149)	114 (86-173)	93 (66-111)	90 (75-109.5)
Mean heparin dose during ECMO (un/kg/hr)	22.5 (20-28)	27 (22.5-32.3)	28 (19-36.5)	20 (20-28)	20 (18-28)	20 (18-29)
Survival to discharge (yes)	85% (17)			72% (8)		
ECMO: Extracorporeal membrane oxygenation, VV: Venovenous, VA: Venoarterial, PTT: Partial thromboplastin time, PPHN: Persistent pulmonary hypertension of the newborn, ARDS: Acute respiratory distress syndrome, eCPR: Extracorporeal cardiopulmonary resuscitation						

Table II. Peak CAR disruption across ECMO time periods and demographic groups		
	Peak CAR disruption Median (IQR)	**p value**
Neonate vs. child	18.4 (8.6-34.9)	0.09
VV vs. VA ECMO	7.5 (0.4-25)	0.32
eCPR vs. other	17.5 (6.5-34.9)	0.53
Pre-cannulation	13.5 (13.5-25.9)	0.03
Peri-cannulation	5.9 (5.7-20.2)	0.85
Post-cannulation	35 (26.7-34.2)	0.29
ECMO: Extracorporeal membrane oxygenation, VV: Venovenous, VA: Venoarterial, IQR: Interquartile range, CAR: Cerebral autoregulation, eCPR: Extracorporeal cardiopulmonary resuscitation		

Table III. Comparison of CAR disruption in the pre-cannulation period across demographic groups		
	Peak CAR disruption Median (IQR)	**p**
Age		0.09
Neonate	6.0 (0.75-35)	
Child	18 (8.6-34.9)	
Type of ECMO		0.32
VV	7.5 (0.43-24.88)	
VA	16.5 (6-34.91)	
eCPR		0.53
Yes	7.5 (5.2-31.4)	
No	17.5 (6.5-34.9)	

ECMO: Extracorporeal membrane oxygenation, VV: Venovenous, VA: Venoarterial, IQR: Interquartile range, CAR: Cerebral autoregulation, eCPR: Extracorporeal cardiopulmonary resuscitation

Discussion

The current study investigated the relationship between impaired CAR and the development of severe neurologic injury in pediatric ECMO patients. The mean burden of impaired CAR did not vary across ECMO time periods and was not associated with neurologic injury. However, shorter (1 hr) periods of highly impaired CAR were more common in the pre-cannulation period and were associated with severe neurologic injury. This aligns with our clinical understanding that shorter periods of more profound clinical instability may confer greater risk of injury than modest physiologic derangements over longer time periods. Further, we found no significant differences in ventilator, laboratory or anticoagulation parameters between the severe and no/minimal injury groups, implying that other factors may play an important role in the development of neurologic injuries acquired on ECMO.

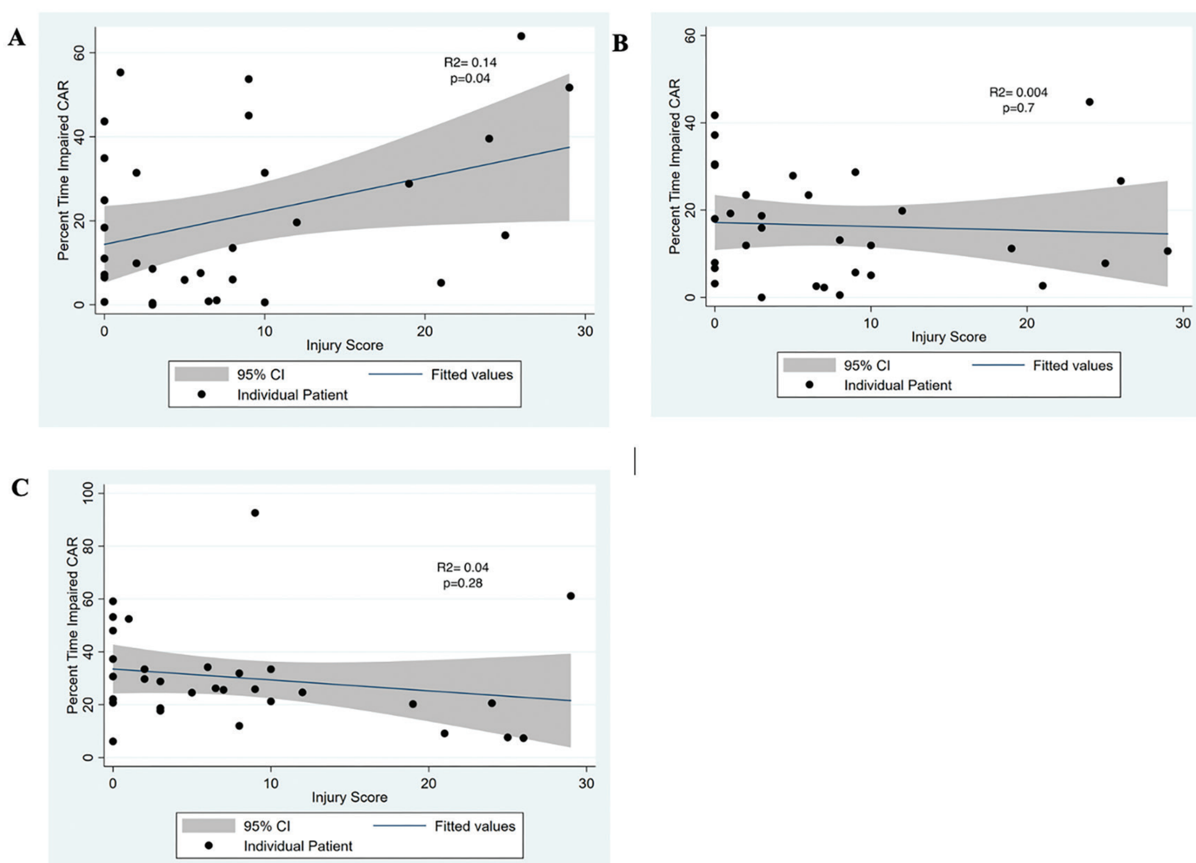

Figure 2. Association between the percentage of time with impaired CAR and the development of neurologic injury seen on neuroimaging in the **A)** pre-cannulation (-24 h to 0 h), **B)** peri-cannulation (0 h to 12 h), **C)** post-cannulation (12h to 72h) period of ECMO support. Neurologic injury scores range from 0-30 with scores >9 correlating with severe neurologic injury. There was a statistically significant correlation between peak autoregulation disruption in the pre-cannulation period and the development of neurologic injury seen on neuroimaging for those with severe injury ($R2=0.14$, $p=0.04$)
ECMO: Extracorporeal membrane oxygenation, CAR: Cerebral autoregulation, CI: Confidence interval

CAR was measured by performing a WTC analysis of MAP and cerebral oximetry as a surrogate for cerebral blood flow. This methodology has been utilized in pediatric patients supported on ECMO, pediatric cardiac arrest and neonatal hypoxic ischemic encephalopathy (10,26,27). Our results compliment these prior studies through utilization in a larger cohort of ECMO patients. Additionally, we utilized WTC in shorter time windows in order to analyze peak periods of impaired CAR. Consistent with prior reports, we found that disruption of CAR correlates with the development of severe neurologic injury for pediatric patients on ECMO (8-10,12,20,26). It has been previously reported that the majority of acute neurologic events occur within the first 24 hours of ECMO initiation, and this is a critical time for CAR disruption (8). Several mechanisms have been proposed to explain this phenomenon including alterations in the pulsatile blood flow pattern (16) and the rapid correction of carbon dioxide which occurs with ECMO initiation (9,13,14). However, prior to cannulation, all patients experienced critical illnesses which themselves are risk factors for CAR disruption and neurologic injury (28-32). To the best of our knowledge, this is the first study to investigate the time-period of maximal disruption of CAR and its impact on the development of neurologic injury for pediatric patients supported on ECMO.

We initially suspected that CAR would be maximally disrupted during the peri-cannulation period given the rapid changes in physiologic status during the cannulation process. However, our data supports the idea that disrupted CAR in the 24 hours preceding ECMO support confers the greatest risk of developing severe neurologic injury. This finding is likely reflective of the patient's underlying critical illness. Cerebral blood flow and cerebrovascular reactivity can be profoundly deranged in various pathophysiologic states such as sepsis (32), severe hypoxemia or acidemia (33). Similarly, in this study, patients with sepsis, PPHN, and congenital heart disease had profound disruption of CAR in the pre-cannulation period. Notably, most patients with severe injury were those who were cannulated with ongoing cardiopulmonary resuscitation. CPR may overlap between the pre- and peri-cannulation periods, making interpretation of peak impaired CAR between time periods difficult to assess in these patients. Clearly, patients cannulated during cardiopulmonary resuscitation are at particular risk for disrupted CAR and neurologic injury. Cessation of forward blood during cardiac arrest can lead to hypoxic ischemic brain injury and cytotoxic edema. CAR is often dysfunctional or absent following cardiac arrest (29,30) and the rapid restoration of cerebral blood flow by VA-ECMO may exacerbate reperfusion injury (28). Overall, the eCPR population represents a high-risk group which requires particular attention in clinical practice and future studies.

It has been well reported that rapid fluctuations of $PaCO_2$ can cause disruption of CAR leading to hemorrhagic injury (9,13,14). In an ELSO registry review, Shah et al. (13) found that pediatric patients who experienced a relative decrease of >30% in ΔCO_2 or had a relative increase ΔMAP >50% immediately following ECMO initiation had increased rates of neurologic complications and hospital mortality. Conversely, the patients in this study experienced a relative decrease of ~25% ΔCO_2 and there was no significant difference in blood gas parameters or maximal correction of blood gas parameters during the peri-cannulation period between the injury and no/minimal injury groups. This may explain why disruptions of CAR in the peri-cannulation period were not found to correlate with severe neurologic injury. Future studies should seek to replicate these findings across multiple sites in order to account for practice variations.

Study Limitations

This study was limited to retrospective data from a single center with a small sample size. These limitations may have confounded study results and also limit its generalizability. The primary outcome of neurologic injury defined by neuroimaging resulted in the exclusion of many patients as the neuroimaging was inconsistently obtained. Due to critical illness or death, certain patients with neurologic injury may not have received imaging. Thus, the risk of omitting an important cohort of patients who suffered neurologic injury from this analysis was present. Additionally, there was often a delay between obtaining imaging and the occurrence of dysregulation, possibly confounding the results. Furthermore, excluding those patients who did not have cerebral oximetry or blood pressure data available may have created a selection bias for children who were more severely ill. Variables were pre-selected, but due to sample size limitations, only univariate analyses were performed. In addition, in certain populations, such as those patients who were cannulated for eCPR, it was difficult to delineate whether the disruption in autoregulation was contributory versus being a response to the cerebral injury.

Conclusion

The 24 hours preceding ECMO support represents a critical window for neuroprotection in pediatric patients. This provides physicians with an opportunity to adapt management strategies in order to avoid periods of impaired CAR which may contribute to subsequent neurologic injury. The current study, along with prior work, demonstrates the value of continual assessment of CAR for pediatric ECMO patients. In the future, bedside interpretation of CAR may be key to improved cerebral protection before and during ECMO support.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the University of Texas Southwestern Medical Center Institutional Review Board (approval number: STU-2023-0788, date: 28.08.2023).

Informed Consent: Retrospective cohort study.

Footnotes

Authorship Contributions

Concept: C.C., D.B., L.R., E.S., Design: C.C., D.B., L.R., E.S., Data Collection or Processing: C.C., S.I., H.L., M.T., D.B., L.R., E.S., Analysis or Interpretation: C.C., S.I., H.L., S.S., M.M., D.B., L.R., E.S., Literature Search: C.C., E.S., Writing: C.C., S.I., H.L., S.S., M.M., M.T., D.B., L.R., E.S.

Conflict of Interest: The authors declare that there is no conflict of interest regarding this study.

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