# Changes in autonomic function and cerebral and somatic oxygenation with arterial flow pulsatility for children requiring veno-arterial extracorporeal membrane oxygenation☆

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## ARTICLE INFO

## ABSTRACT

*Background:* Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) carries variability in arterial flow pulsatility (AFP).
*Research question:* What changes in cerebral and somatic oxygenation, hemodynamics, and autonomic function are associated with AFP during VA-ECMO?
*Methods:* This is a prospective study of children on VA-ECMO undergoing neuromonitoring. AFP was quantified by arterial blood pressure pulse amplitude and subcategorized: no pulsatility ($<1$ mmHg), minimal pulsatility (1 to $<5$ mmHg), moderate pulsatility (5 to $<15$ mmHg) and high pulsatility ($\geq15$ mmHg). CVPR was assessed using the cerebral oximetry index (COx). Cerebral and somatic oxygenation was assessed using cerebral regional oximetry ($rSO_2$) or peripheral oxygen saturation ($SpO_2$). Autonomic function was assessed using baroreflex sensitivity (BRs), low-frequency high-frequency (LF/HF) ratio and standard deviation of heart rate R–R intervals (HRsd). Differences were assessed across AFP categories using linear mixed effects models with Tukey pairwise comparisons. Univariate logistic regression was used to explore risk of AFP with brain injuries.
*Results:* Among fifty-three children, comparisons of moderate to high pulsatility were associated with reductions in $rSO_2$ ($p < 0.001$), SpO 2 ($p = 0.005$), LF/HF ratio ($p = 0.028$) and an increase in HRsd ($p < 0.001$). Reductions in BRs were observed across comparisons of none to minimal ($P < 0.001$) and minimal to moderate pulsatility ($p = 0.004$). Comparisons of no to low pulsatility were associated with reductions in BRs ($p < 0.001$) and ABP ($p < 0.001$) with increases in $SpO_2$ ($p < 0.001$) and HR ($p < 0.001$). Arterial ischemic stroke was associated with higher pulsatility ($p = 0.0384$).
*Conclusion:* During VA-ECMO support, changes toward high AFP are associated with autonomic dysregulation and compromised cerebral and somatic tissue oxygenation.

## 1. Introduction

Extracorporeal membrane oxygenation (ECMO) is a life-sustaining therapy for critically ill patients who experience refractory heart or lung failure (Jenks et al., 2017). Veno-arterial (VA) ECMO support is typically used with the primary goal of providing cardiac support, whereas veno-venous (VV) ECMO support is primarily used during refractory pulmonary failure (Felling et al., 2023). The use of ECMO support in critical care has increased worldwide, but with it comes a high risk of neurologic injury (Tian et al., 2020; Okochi et al., 2018). Amongst surviving children who undergo ECMO support, long-term neurodevelopmental impairments can ensue (IJsselstijn et al., 2018; Sadhwani et al., 2019). An improved understanding of factors surrounding ECMO physiology that relate to neurologic injury and long-term morbidity are key to understanding how to prevent or mitigate against such complications.

Regulation of cerebral blood flow is important for brain homeostasis during critical illness and is an important factor during ECMO support to reduce long-term neurologic morbidity (Donnelly et al., 2016). A variety of factors may alter such cerebral blood flow regulation in the setting of VA-ECMO support, including baseline compromise of cerebral perfusion during the refractory cardiac failure preceding ECMO initiation, as well as potential alterations in the direction of flow when arterial cannulation is directed into the right carotid artery (Lohrer et al., 1992). During V-A ECMO support, systemic arterial flow pulsatility (AFP) can vary substantially. This may be the result of the cannulation site or blood being pumped into the arterial circulation bypassed from the heart's natural activity. However, changes in cardiac output or ECMO pump flow rates can influence systemic AFP in a dynamic fashion throughout a patient's ECMO run (Felling et al., 2023). There is some evidence that non-pulsatile V-A ECMO flow can be associated with disturbances in cerebrovascular pressure reactivity (CVPR) (O'Neil et al., 2012; Veraar et al., 2019), but limited evidence exists regarding how cerebral oxygenation ($rSO_2$), systemic hemodynamics, autonomic function and CVPR change across fluctuations in systemic AFP.

In this study, we aimed to investigate the association of systemic AFP with changes in cerebral regional oximetry ($rSO_2$) and peripheral oxygen saturation ($SpO_2$), autonomic function, hemodynamics and CVPR for children requiring VA ECMO support.

## 2. Materials and methods

Study design: This is a secondary analysis of a single-center prospective observational study at Phoenix Children's Hospital which enrolled consecutive patients ages 0–18 years of age who required ECMO support and underwent multimodality neuromonitoring (MMM) from June 2019 to April 2022. As part of this study, patients underwent MMM that included cerebral $rSO_2$ and peripheral oxygen saturation ($SpO_2$), mean arterial blood pressure (MAP) and heart rate (HR). All of these measures were collected continuously and monitored at all times during each ECMO run. Patients also underwent a daily transcranial doppler ultrasound (TCD) assessment, in addition to continuous electroencephalography, although these modalities were not analyzed for this secondary analysis. This secondary analysis focused on children undergoing V-A ECMO support, with exclusion of patients undergoing V–V ECMO support. Patients were also excluded in case of prior known acquired brain injury, sickle cell disease and Moya-Moya disease. The study was approved by the Phoenix Children's Institutional Review Board (No: 19–257). Written informed consent was obtained from parents or legal guardians for each participant.

The primary outcome variables were cerebral $rSO_2$ and $SpO_2$ as measures of cerebral and somatic tissue oxygenation, respectively. To assess for hemodynamics, we also investigated MAP and heart rate HR. To assess for autonomic function, we investigated baroreflex sensitivity (BRs) and two measures of heart rate variability: low-frequency high-frequency (LF/HF) ratio and heart rate standard deviation of R–R intervals (HRsd). The independent predictor variable was systemic AFP, described by the arterial blood pressure pulse amplitude (aABP). Patient level characteristics obtained included demographic and ECMO-circuit data such as age, race, sex, ECMO course duration, cannulation site, pump flow rates, arterial and venous catheter sizes, acute brain injuries (including arterial ischemic stroke, hemorrhagic stroke, and hypoxic ischemic brain injury), in-hospital mortality, and in-hospital mortality related to acute brain injuries.

As part of this study, patients underwent MMM that included cerebral $rSO_2$. MMM and systemic hemodynamic monitoring data were integrated through a multimodality neurologic monitoring device (CNS200®; Moberg Intensive Care Unit (ICU) Solutions®, Philadelphia, PA). Intensive Care Monitor Plus (ICM+®) software (Cambridge, UK) was used to visualize and process all MMM data and calculate model-based indices of cerebrovascular pressure reactivity (CVPR) and autonomic function (AF). Physiologic data were collected from ECMO initiation to decannulation. Arterial blood pressure (ABP) was continuously monitored from an indwelling radial or femoral catheter. Near infrared spectroscopy sensors were placed on the bifrontal forehead and $rSO_2$ was continuously measured (Medtronic INVOS®). Data with substantial artifacts observed through visual analysis were removed.

Theory/Calculation: CVPR was investigated using the cerebral oximetry index (COx) (Kirschen et al., 2021; Rosenblatt et al., 2020; Healy et al., 2019), which represents a moving Pearson correlation coefficient of ABP and $rSO_2$. COx is calculated within a 5-min averaging window updated every 60 s. COx values approaching 1 are postulated to represent inefficient CVPR, whereas values that are negative or approaching 0 are postulated to represent efficient CVPR. BRs was calculated with a modification of the sequential cross-correlation method that has been described previously (Westerhof et al., 2004; Sykora et al., 2019a; Appavu et al., 2021). The applied function uses systolic peaks of ABP to create R–R interval time series using an automated detection algorithm. From this, the slope of the linear regression between 10-s series of R–R intervals and the corresponding 10-s series of systolic blood pressure was calculated. A cross-correlation function was used to determine the maximal correlation coefficient and remove the influence of unknown time delay of the baroreceptor response. The slope returned was adjusted to the correlation coefficient to compensate for the influence of uncorrelated noise, and the subsequent BRs calculated value was updated every 10 s and expressed in milliseconds per millimeter of mercury (ms/mmHg). BRs values are thought to represent the responsiveness of baroreflex receptors, which are responsible for regulating blood pressure and cardiovascular function. For all heart rate variability measures, a 30-s time series of R–R intervals was assessed from electrocardiogram activity updated every 10 s. HRsd was computed in the time-domain whereas LF/HF ratio was computed in the frequency domain, using Lomb-Scargle periodogram (No authors listed, 1996). The LF/HF ratio was used to assess sympathovagal balance reflecting sympathetic and parasympathetic activity (low-frequency component) as compared to parasympathetic activity (high-frequency component). The LF/HF ratio was calculated by taking the spectral power in R–R low frequency (0.04–0.15 Hz) and dividing it by high frequency (0.15–0.4 Hz). HRsd was used to evaluate overall heart rate variability (Kleiger et al., 2005).

Statistical analysis: Descriptive characteristics were summarized by using median and interquartile range (IQR) or counts and percentages as appropriate. Based on the distribution of aABP values across all patients, aABP was stratified into four groups: no pulsatility (0 to < 1 mmHg, minimal pulsatility (1 to < 5 mmHg), moderate pulsatility (5 to < 15 mmHg), and high pulsatility ($\geq$15 mmHg). We performed a mixed effects model with the subject as the random effect and an autoregressive order of 1 to model for the observations within subjects. The Tukey pairwise comparison test was used to evaluate for differences is least squares (LS) means estimates of physiologic variables across each category of pulsatility, accounting for multiple comparisons. To explore the relationship of aABP to neurologic injury and ECMO characteristics

at the subject level, we performed univariate logistic regression to evaluate the median aABP value for each patient with subject-related outcomes such as death, acute brain injuries, or death related to acute brain injuries. Acute brain injuries included arterial ischemic stroke (AIS), hemorrhagic stroke (HS) and hypoxic ischemic brain injury (HIBI). Univariate linear regression was used to investigate the relationship with of median aABP values for each patient with their maximal and minimal arterial pump flow rates, and arterial and venous cannulation size. Kruskal-Wallis test was used to determine whether differences exist in median aABP values for each patient with site of arterial cannulation (right carotid artery versus aorta versus femoral artery) or venous cannulation (internal jugular vein versus right atrium versus femoral vein).

## 3. Results

Demographic data is presented in Table 1. Seventy-five children were enrolled in the original study, of which fifty-three children (70.7%) underwent VA-ECMO support. Demographic data of children undergoing VA-ECMO support is described in Table 1. Age ranges from within the first day of birth to eighteen years of age (median 0.6 years, interquartile range (IQR) [0.2, 6.6]). Twenty-nine children (38.7%) on VA-ECMO support were female. Of the fifty-three children undergoing VA-ECMO support, sixteen children (30.2%) experienced acute brain injury, of which five children (31.3%) experienced arterial ischemic stroke, three children (18.8%) experienced hemorrhagic stroke, seven children (43.8%) experienced hypoxic ischemic brain injury, and one child (6.3%) experienced both an arterial ischemic stroke and hypoxic ischemic brain injury. Sixteen children (30.2%) undergoing VA-ECMO support experienced in-hospital mortality, and twelve children (22.6%) undergoing VA-ECMO support experienced acute brain injury and subsequent in-hospital mortality.

Changes in physiologic variables across thresholds of AFP are presented in Table 2 and Fig. 1. Across thresholds of no to low pulsatility, we identified reductions in BRs (estimate $-740.259$, $p < 0.001$) and ABP (estimate $-0.345$, $p < 0.001$) with increases in SpO$_2$ (estimate 0.275, $p < 0.001$) and HR (estimate 2.594, $p < 0.001$). Across thresholds of low to moderate pulsatility, we identified reductions in BRs (estimate $-87.242$, $p = 0.004$) and ABP (estimate $-0.552$, $p < 0.001$) and increases in HR (estimate 4.511, $p < 0.001$) and COx (estimate 0.004, $p < 0.001$). Across thresholds of moderate to high pulsatility, we identified reductions in rSO$_2$ (estimate $-0.053$, $p < 0.001$), SpO$_2$ (estimate $-0.051$, $p = 0.005$), and LF/HF ratio (estimate $-0.166$, $p = 0.028$), and increases in ABP (estimate 0.212, $p < 0.001$), HR (estimate 1.510, $p < 0.001$) and HRsd (estimate $= 0.033$, $p < 0.001$).

Using univariate logistic regression, we did not observe significant associations between aABP to acute brain injury as an aggregate group, or to hemorrhagic stroke, hypoxic ischemic brain injury, in-hospital mortality, or in-hospital mortality related to acute brain injury. However, we did observe that arterial ischemic stroke was associated with

**Table 1**
Patient characteristics and VA-ECMO circuit data.

| Characteristic (n = 53) | n | N% |
| --- | --- | --- |
| Female sex, | 29 | 54.7 |
| Ethnicity | | |
|   Hispanic | 28 | 37.3 |
|   Caucasian | 30 | 40.0 |
|   Native American | 7 | 9.3 |
|   African American | 7 | 9.3 |
|   Asian American | 2 | 2.7 |
| Brain Injury | 16 | 30.2 |
|   AIS | 7 | 13.2 |
|   HS | 3 | 5.7 |
|   HIBI | 7 | 10.7 |
| Arterial Cannulation | | |
|   Carotid artery | 34 | 64.1 |
|   Aorta | 16 | 26.4 |
|   Femoral artery | 3 | 5.6 |
| Venous Cannulation | | |
|   Internal jugular vein | 31 | 58.5 |
|   Right atrium | 14 | 24.0 |
|   Femoral vein | 6 | 11.3 |
| In-Hospital Mortality | 16 | 30.2 |
| In-Hospital Mortality with Brain Injury | 12 | 22.6 |

| | Median | Interquartile Range |
| --- | --- | --- |
| Age (year) | 0.6 | 0.2, 6.6 |
| Arterial catheter size (mm) | 11.0 | 8.0, 15.3 |
| Venous catheter size (mm) | 14.0 | 12.0, 19.0 |
| ECMO duration (days) | 7.4 | 4.0, 12.0 |
| aABP, mmHg | 10.6 | 6.52, 14.4 |
| ABP, mmHg | 66.0 | 57.7, 75.9 |
| HR, bpm | 114.0 | 98.6, 131.7 |
| rSO$_2$, % | 67.9 | 60.0, 75.9 |
| SpO$_2$, % | 96.8 | 92.7, 99.0 |
| COx | 0.0 | (-0.2, 0.3 |
| BRs | 3.8 | 2.1, 7.7 |
| LF/HF Ratio | 1.2 | 0.4, 2.8 |
| HRsd | 1.7 | 0.8, 3.4 |

Abbreviations: AIS, arterial ischemic stroke; HIBI, hypoxic ischemic brain injury; HS, hemorrhagic stroke; ECMO, extracorporeal membrane oxygenation; ABP, arterial blood pressure; HR, heart rate; rSO$_2$, cerebral regional oximetry; SpO$_2$, peripheral oxygen saturation; COx, cerebral oximetry index; BRs, baroreflex sensitivity; LF, low frequency; HF, high frequency; HRsd, heart rate standard deviation of R–R intervals; mm, millimeters; % percent; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; n, count.

**Table 2**
Changes in Physiologic Variables Across aABP Thresholds.

| Changes in physiologic features from no to low pulsatility | | | | |
| --- | --- | --- | --- | --- |
| *Feature* | *Estimate* | *Standard Error* | *p-value* | *95% CI* |
| COx | 0.002 | 0.004 | 0.545 | −0.007, 0.011 |
| rSO$_2$ | −0.003 | 0.027 | 0.999 | −0.072, 0.066 |
| SpO$_2$ | 0.275 | 0.034 | <0.001 | 0.190, 0.361 |
| ABP | −0.345 | 0.024 | <0.001 | −0.405, −0.284 |
| HR | 2.594 | 0.036 | <0.001 | 2.503, 2.685 |
| BRs | −740.259 | 81.648 | <0.001 | −944.116, −536.402 |
| LF/HF Ratio | −0.055 | 0.081 | 0.893 | −0.259, 0.149 |
| HRsd | −0.020 | 0.015 | 0.477 | −0.058, 0.017 |
| HRrmssd | −0.887 | 0.757 | 0.613 | −2.787, 1.014 |

| Changes in physiologic features from low to moderate pulsatility | | | | |
| --- | --- | --- | --- | --- |
| *Feature* | *Estimate* | *Standard Error* | *p-value* | *95% CI* |
| COx | 0.004 | 0.001 | <0.001 | 0.001, 0.007 |
| rSO$_2$ | 0.046 | 0.016 | 0.0181 | 0.006, 0.085 |
| SpO$_2$ | 0.0083 | 0.0154 | 0.999 | −0.038, 0.039 |
| ABP | −0.552 | 0.010 | <0.001 | −0.578, −0.526 |
| HR | 4.511 | 0.021 | <0.001 | 4.458, 4.564 |
| BRs | −87.242 | 26.539 | 0.004 | −153.505, −20.979 |
| LF/HF Ratio | −0.001 | 0.048 | 1.000 | −0.121, 0.120 |
| HRsd | 0.009 | 0.009 | 0.733 | −0.013, 0.030 |
| HRrmssd | −0.159 | 0.442 | 0.982 | −1.269, 0.951 |

| Changes in physiologic features from moderate to high pulsatility | | | | |
| --- | --- | --- | --- | --- |
| *Feature* | *Estimate* | *Standard Error* | *p-value* | *95% CI* |
| COx | −0.002 | 0.001 | 0.184 | −0.004, 0.000 |
| rSO$_2$ | −0.053 | 0.013 | <0.001 | −0.086, −0.019 |
| SpO$_2$ | −0.051 | 0.015 | 0.005 | −0.090, −0.012 |
| ABP | 0.212 | 0.009 | <0.001 | 0.190, 0.235 |
| HR | 1.510 | 0.019 | <0.001 | 1.464, 1.557 |
| BRs | −12.628 | 18.570 | 0.892 | −58.992, 33.736 |
| LF/HF Ratio | −0.166 | 0.061 | 0.028 | −0.262, −0.069 |
| HRsd | 0.033 | 0.006 | <0.001 | 0.018, 0.049 |
| HRrmssd | 0.140 | 0.323 | 0.969 | −0.670, 0.951 |

Abbreviations: aABP, arterial blood pressure pulse amplitude; ABP, arterial blood pressure; HR, heart rate; rSO$_2$, cerebral regional oximetry; SpO$_2$, peripheral oxygen saturation; COx, cerebral oximetry index; BRs, baroreflex sensitivity; LF, low frequency; HF, high frequency; HRsd, heart rate standard deviation of R–R intervals; HRrmssd, heart rate root mean square standard deviation of R–R intervals.
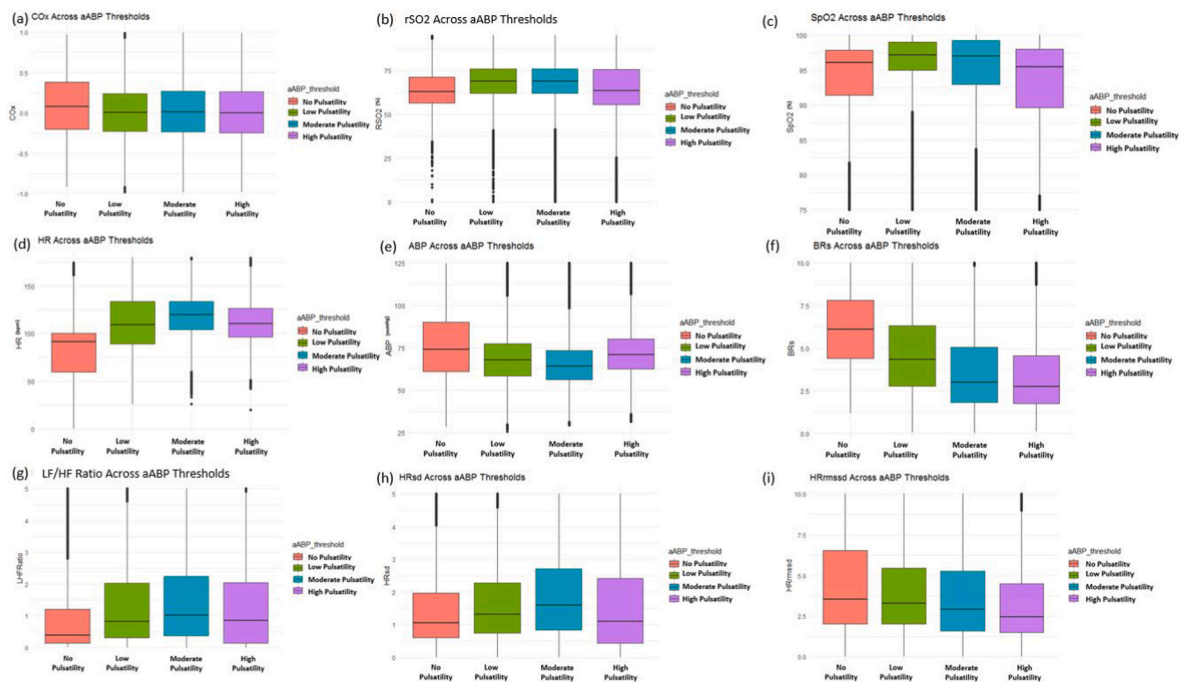
**Fig. 1.** Boxplots of Changes in Physiologic Variables Across aABP Thresholds
Abbreviations: aABP, arterial blood pressure pulse amplitude; ABP, arterial blood pressure; HR, heart rate; rSO$_2$, cerebral regional oximetry; SpO$_2$, peripheral oxygen saturation; COx, cerebral oximetry index; BRs, baroreflex sensitivity; LF, low frequency; HF, high frequency; HRsd, heart rate standard deviation of R–R intervals; HRrmssd, heart rate root mean square standard deviation of R–R intervals.

higher median aABP values (odds ratio = 1.24 [95% CI, 1.03–1.55], p = 0.0384), with age, sex and race excluded as confounding or interacting factors (Table 3). We did not identify that aABP was associated with maximal or minimal arterial or venous cannulation sizes or arterial pump flow rates (Supplemental Table 1). We also did not observe differences in aABP values based on varying sites of arterial or venous cannulation (Supplemental Table 2 and Supplemental Fig. 1).

## 4. Discussion

This study evaluated physiologic and patient-level characteristics associated with systemic AFP in children undergoing VA ECMO support. Here, we identified a unique pattern of changes in autonomic function, hemodynamics, and cerebral and somatic oxygenation across varied degrees of AFP. To our knowledge, this is the first study to investigate physiologic changes observed across systemic AFP in children requiring V-A ECMO support.

A complex interplay exists regarding arterial flow dynamics and its relationship to regulation of blood flow and capillary tissue exchange. Regulation of cerebral blood flow is thought in most patient populations to be primarily driven through smooth muscle control of the cross-sectional area of small vessel arterioles with an assumption that other factors influencing cerebrovascular impedance are minimal. The V-A ECMO population is unique in this regard, as varying degrees of systemic AFP during V-A ECMO support offers potential insights into the effects of vascular impedance (O'Neil et al., 2012; Veraar et al., 2019; Varsos

et al., 2014). Non-pulsatile arterial flow represents a steady state condition in which blood flow acts as a direct current without the factor of vascular impedance, where arterial compliance is saturated and through Hagen-Poiseuille principles, resistance of cerebral blood flow may be directly related to the relationship of cerebral perfusion pressure and the cross-sectional area of cerebral small vessel arterioles (De Riva et al., 2012). When arterial flow pulsatility is introduced, blood flow then acts as an alternating current and vascular impedance enters the picture (De Riva et al., 2012; O'Rourke and Taylor, 1967). With pulsatile arterial flow, resistance to blood flow is additionally modulated by compliance of the vascular bed and heart rate, which each relating to impedance of flow (Varsos et al., 2014; De Riva et al., 2012; O'Rourke and Taylor, 1967).

The relationship of cerebrovascular impedance to autonomic function is complex, but findings in this study offer insights into its contribution. The transition from no to low pulsatility was associated with a rise in SpO$_2$, suggesting that the introduction of vascular impedance to blood flow may be somewhat beneficial to somatic capillary exchange. In the transitions from no to low pulsatility and low to moderate pulsatility, we further identified reductions in ABP and BRs and corresponding increases in HR. The transition from moderate to high pulsatility, however, was not associated with a significant change in BRs, and both HR and ABP increased with corresponding reductions in cerebral rSO$_2$ and peripheral SpO$_2$. Heart rate variability measures did not change across no to low pulsatility or low to moderate pulsatility, but a reduction in the LF/HF ratio and an increase in HRsd was observed

**Table 3**
Association of acute brain injuries with ABP pulse amplitude.

| Variable | ABI | | AIS | | HS | | HIBI | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | OR (95% CI) | *p* value | OR (95% CI) | *p* value | OR (95% CI) | *p* value | OR (95% CI) | *p* value |
| ABP Pulse Amplitude (mmHg) | 1.06 (0.94, 1.21) | 0.3160 | **1.24 (1.03, 1.55)** | **0.0390** | 0.97 (0.76, 1.23) | 0.7810 | 1.01 (0.85, 1.20) | 0.9166 |

Abbreviations: ABI, acute brain injury; AIS, arterial ischemic stroke; ABP, arterial blood pressure; HS, hemorrhagic stroke; HIBI, hypoxic ischemic brain injury; OR, odds ratio; CI, confidence interval; mmHg, millimeters of mercury.

across moderate to high pulsatility. BRs represents the first line of defense in preserving cerebral blood flow and is primarily a measure of how heart rate and vascular resistance change in response to blood pressure (La Rovere et al., 2008). High BRs suggests robust and efficient regulation of systemic arterial blood pressure, while low BRs may suggest compromised ability to maintain blood pressure stability. Prior work has demonstrated that lower BRs is associated with infections after arterial ischemic stroke (Sykora et al., 2019b) and worsened outcomes in children with hemorrhagic stroke from cerebrovascular arteriovenous malformations (Appavu et al., 2021) and adults with traumatic brain injury (Sykora et al., 2016) and aneurysmal subarachnoid hemorrhage (Nasr et al., 2018). The physiologic alterations we identified suggests that in the transition to high pulsatility, increases in ABP and HR with low and inefficient BRs may reflect high cardiovascular workload with worsened cerebral and somatic oxygenation. Furthermore, the reduction the LF/HF ratio with an increase in HRsd may suggests that there is an increased parasympathetic influence or aberrant sympathetic modulation during this transition. Overall, these changes toward high pulsatility suggest dysregulated autonomic function and compromised oxygenation in cerebral and somatic tissues. Such findings may highlight the importance of optimizing ECMO settings and flow pulsatility to maintain adequate perfusion, oxygenation and autonomic balance for children requiring VA-ECMO support.

We did not observe robust changes in CVPR in our study utilizing COx, although we did observe a mild increase in COx values across the transition from low to moderate pulsatility. It remains unclear regarding the extent to which changes in cerebrovascular impedance influence the CVPR efficiency, and techniques utilizing more direct measures of cerebral blood flow, such mean velocity index calculations from transcranial Doppler ultrasound, may be more insightful to investigate this relationship (Budohoski et al., 2012). While we did not observe ECMO pulsatility to be associated with overall acute brain injuries, we did observe an association with higher arterial flow pulsatility with the incidence of arterial ischemic stroke. Further work may be necessary to further investigate this relationship to identify whether high arterial flow pulsatility predisposes patients on VA-ECMO support to arterial clot formation and propagation.

Changes in AFP can be multifactorial in nature, resulting from either from management strategies used during ECMO support, or from the underlying physiologic health of the patient. In terms of settings, changes in ECMO flow rate, which is determined by pump speed can be influential, with higher flow rates often resulting in more continuous flow and reduced pulsatility. Sweep gas flow rates in the ECMO oxygenator can influence oxygen delivery and consequently, have an influence in arterial flow characteristics. Clinical management strategies, such as the use of vasoactive agents, may also influence arterial flow patterns. In terms of underlying physiologic health, reduced ventricular afterload and changes in native cardiac function can lead to diminished AFP. In the setting of severe cardiac dysfunction, AFP can be minimal or not present. Complications such as thromboses, kinking of cannulas or malpositioning can also impact AFP. As a secondary analysis, our study was not designed to identify specific factors that changed AFP in specific patients. Our findings, however, are hypothesis generating that factors that influence AFP, whether they arise from clinical management strategies or underlying physiologic function, may influence autonomic function and cerebral and somatic oxygenation and warrant further investigation.

Our study carries its limitations. Because this is a secondary analysis of a prospective study, it was not designed to select and identify for patients where AFP was minimally influenced by underlying ECMO circuit characteristics. Our subject-level analysis of relationships of AFP to characteristics such as cannulation site and pump flow rates, however, suggest that these may not have played a significant role. Our study was observational in nature and did not assess whether interventions that altered VA-ECMO AFP directly changed biomarkers reflecting cerebral and systemic physiology, or vice-verse. Our use of a single-site study design with a relatively small sample size limits generalizability of our study results or multivariable analysis of specific acute brain injury cohorts. Larger multicenter work with larger sample sizes that directly evaluate for interventions that lead to ECMO AFP variation, and that evaluates cerebral and systemic physiology during such events, may be helpful toward validating our findings.

## 5. Conclusion

In children undergoing VA-ECMO support, transitions toward high AFP may be associated with autonomic dysregulation and compromised oxygenation to cerebral and somatic tissues. Optimization of ECMO settings toward more optimal AFP may aid in providing adequate perfusion, oxygenation, and autonomic homeostasis for these critically ill patients.

## Authorship

BA provided substantial contributions to the conception and design of the study, acquisition, and analysis of data, and drafting significant portions of the manuscript All authors (BA, ED, KH, DH, and TA) have participated in a meaningful way to the manuscript in data collection, conception, analysis and drafting of the manuscript. All authors provide final approval of the version to be published.

## Conflicts of interest

Dr. Appavu reports a completed research grant from Moberg ICU Solutions as well as a research grant from the United States Department of Defense Congressionally Directed Medical Research Programs Epilepsy Research Program (W81XWH-19-1-0514), both outside the scope of this work. Dr. Appavu also received speaking honoraria from Natus® for two webinar presentations. Dr. Appavu is also an editorial board member for the journal, Neurocritical Care. All other authors have no conflicts of interest.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Brian Appavu, MD reports financial support was provided by American Heart Association. Brian Appavu, MD reports a relationship with Natus Medical Inc that includes: speaking and lecture fees. Dr. Appavu is also an editorial board member for the journal, Neurocritical Care. Dr. Appavu also reports a completed research grant from Moberg ICU Solutions as well as a research grant from the United States Department of Defense Congressionally Directed Medical Research Programs Epilepsy Research Program (W81XWH-19-1-0514), both outside the scope of this work.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bas.2023.102731.

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