Peri-Operative Cerebral Regional Oxygen Saturation Variability and Short-Term Outcomes Following Cardiac Surgery in Neonates

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Impact Statement:

- Cerebral regional oxygen saturation ($crSO_2$) is a marker of cerebral perfusion autoregulation

- Low post-operative $crSO_2$ variability in neonates with aortic arch obstruction is associated with poorer neurodevelopmental outcomes
- Several factors including peri-operative perfusion technique affect post-operative $crSO_2$ variability
- The relationship between pre-operative and post-operative crSO2 variability is unknown

ABSTRACT

Decreased post-operative cerebral region oxygenation saturation ($crSO_2$) variability, a surrogate for cerebral autoregulation, correlates with poor neurodevelopmental outcomes in neonates who undergo cardiac surgery. The goal of this study is to investigate the relationship between pre- and post-operative $crSO_2$ variability in neonates requiring neonatal cardiac surgery for congenital heart disease (CHD).

The variability of averaged 1-min $crSO_2$ values was calculated for a minimum of 12h before and for the first 48h following cardiac surgery with cardiopulmonary by-pass in neonates between November 2019 and May 2021.

The $crSO_2$ variability increased by 9% with each additional postnatal day in the pre-operative monitoring period ($p=0.009$). There was a 40% decrease in $crSO_2$ variability between the pre-and post-operative monitoring periods ($p<0.001$). There were no associations between the degree of decrease in $crSO_2$ variability and CHD classification (aortic arch obstruction or single ventricle physiology).

The $crSO_2$ variability improves with each additional postnatal day but then decreases by almost half following cardiac surgery in neonates. We did not observe any association between pre-operative $crSO_2$ variability and post-operative ventilator-free days, post-operative ICU days, or mortality. The long-term effects or significance of reduced $crSO_2$ require further exploration.

INTRODUCTION

Near infrared spectroscopy (NIRS) has been in use for more than four decades in the field of critical care and is increasingly used in the neonatal intensive care unit (NICU).[1] NIRS allows for the non-invasive monitoring of tissue oxygenation based on the physiologic property of light adsorption of hemoglobin at different wavelengths and provides a surrogate for blood flow and its fluctuations. A major clinical application of NIRS is the peri-operative monitoring of neonates with congenital heart disease (CHD).[2, 3]

While the childhood mortality of patients with CHD has significantly decreased, neurodevelopmental impairments remain one of the most common complications affecting survivors of CHD. [4,5] As such, the identification of patient-specific risk factors and/or modifiable management strategies to improve outcomes in neonates undergoing neonatal cardiac surgery is a high research priority. [6, 7]

Few studies have explored the absolute trends in cerebral regional oxygen saturation ($crSO_2$) in infants prior to surgery for CHD. These studies indicate that pre-operative $crSO_2$ is lower in infants with CHD compared to healthy controls, especially in those with left-sided obstructive lesions.[8-10] Evidence also supports an association between peri-operative $crSO_2$ and neurodevelopmental outcomes in infants with CHD.[11] However, there remains significant gaps in knowledge regarding postnatal baseline $crSO_2$ normal range as well as its impact on neurodevelopmental outcomes in neonates with CHD.

Beyond absolute $crSO_2$ trend, $crSO_2$ variability, which indirectly reflect cerebral autoregulation, sheds light into cerebral perfusion.[12] Previous studies have found correlations between cerebral NIRS wave variability and blood pressure variability in preterm infants as well as a strong correlation between slow cerebral NIRS waveform and slow transcranial doppler in neonates with sepsis.[13.14] Changes in $crSO_2$ variability, specifically a decrease in post-operative $crSO_2$ variability amongst survivors of CHD surgery, have been linked with poor neurodevelopmental outcomes particularly in neonates with aortic arch obstruction repair.[3,15]

The goal of this study is to investigate the relationship between pre- and post-operative $crSO_2$ variability in a cohort of neonates undergoing cardiac surgery for CHD. The quantification of $crSO_2$ variability during the peri-operative period is important to better understand the impact of pre- and post-operative factors (e.g., perfusion technique) on $crSO_2$ variability and outcomes in this high-risk population.

METHODS

This study was approved and exempted from a full review by the Institutional Review Board (IRB) at the University Of Virginia School Of Medicine. A patient consent requirement was also waived by the Institutional Review Board (IRB) at the University of Virginia School of Medicine. Every aspect of this research was performed in accordance with relevant guidelines/regulations. We included neonates (<30 days of age on admission and ≥ 35 weeks' gestation at time of delivery) that underwent cardiac surgery with cardiopulmonary by-pass (CPB) in the first 30 days after birth from November 2019 to May 2021. All patients underwent bi-caval venous cannulation and those patients requiring neonatal arch repair underwent anterograde cerebral perfusion (ACP), with either brief or no exposure to deep hypothermic circulatory arrest (DHCA).

Pre-operative $crSO_2$ monitoring took placed either in the NICU or in the pediatric intensive care unit (PICU), no earlier than the second day after birth and for a minimum period of 12h. Post-operative $crSO_2$ monitoring occurred in the PICU for the first 48h following surgery. The $crSO_2$ values were continuously captured using either the Foresight Elite® tissue oximeter (Edwards Lifesciences, Irvine, CA) for patients who had their pre-operative monitoring in the NICU, or the INVOS™ 5100C® cerebral oximeter (Medtronic, Minneapolis, MN) for all infants cared for in the PICU. crSO2 values were averaged over 1-min intervals and $crSO_2$ variability was calculated using the root mean of successive squared differences (RMSSD) for both the pre- and post-operative phases of monitoring as previously described.[3] In practical terms, the RMSSD measures the amount of change in $crSO_2$ from minute-to-minute over the course of a specified period. Missing $crSO_2$ values were imputed using predictive mean matching. To characterize changes in $crSO_2$ variability over time, we also calculated a 60-min moving average measure for each minute of monitoring using the RMSSD from the previous 60 min.

Patient and clinical characteristics were collected, including age at time of admission to the NICU, age at time of pre-operative $crSO_2$ monitoring start, age at time of surgery, weight at admission and time of surgery. In addition, patients were assigned to one of four previously described diagnostic classes of CHD: class 1—two ventricle physiology without aortic obstruction, class 2—two ventricle physiology with aortic obstruction, class 3—single ventricle physiology without aortic obstruction, or class 4—single ventricle physiology with aortic obstruction.[16]

The primary clinical outcomes of interest were ventilator-free days, defined as the number of days without invasive mechanical ventilation following surgery to post-operative day 28, with

patients who died before day 28 while on mechanical ventilation assigned zero, mortality, post-operative seizures, and post-operative ICU days.

Distribution of continuous variables were assessed using the Wilk-Shapiro test for normality. Continuous variables were compared using Student's *t* test, Wilcoxon signed rank test, or linear regression as appropriate. Pre- and post-operative $crSO_2$ measures were matched at the patient level and compared using paired difference *t* test or Wilcoxon matched-pairs signed rank test as appropriate. Categorical variables were compared using chi-square test or Fisher exact test as appropriate. Type I error was set at 0.05. All calculations were performed using STATA/IC 12.1 (STATA Corporation, College Station, TX).

RESULTS

Cohort characteristics

Thirty-seven neonates were included in the study with a median of 7 days of age (interquartile range (IQR) 6-10 days) at the time of surgery. The cohort's demographic and clinical characteristics are described in Table 1.

Primary Outcomes

We did not observe any association between pre-operative $crSO_2$ variability and post-operative ventilator-free days, post-operative ICU days, or mortality (Table 1).

Pre-operative $crSO_2$

The median age at the start of pre-operative $crSO_2$ monitoring was 4 days (IQR 2 - 5 days). We observed an increase in the $crSO_2$ variability of 9% with each additional day after birth in the pre-operative monitoring period ($p=0.009$). There were no differences in pre-operative $crSO_2$

variability based on CHD classification: aortic arch obstruction (classes 2 and 4) or single ventricle physiology (classes 3 and 4). There were no differences in types of cardiac lesion or clinical characteristics between patient monitored pre-operatively in the NICU versus PICU (or based on monitor used).

The $crSO_2$ variability was 31% lower in patients receiving invasive mechanical ventilation during the pre-operative monitoring phase ($p=0.04$). $crSO_2$ variability was not affected by the need for continuous infusions for pain and/or sedation ($p=0.25$).

Post-operative $crSO_2$

Variability of $crSO_2$ decreased by 40% between the pre- and post-operative monitoring period ($p<0.001$). There were no associations between the degree of decrease in $crSO_2$ variability and CHD classification (aortic arch obstruction vs. single ventricle physiology). There were no differences in the mean absolute $crSO_2$ values between the pre- and post-operative periods (72% vs 74%). The time series plots of pre- and post-operative $crSO_2$ values and corresponding $crSO_2$ variability for a representative neonate are shown in Figure 1.

Table 1. Patient demographics and clinical characteristics.

Characteristics	n (%)
Age at time of surgery (days)	7 (IQR 6 – 10)
Gestational age (weeks)	39 (IQR 38 - 39)
Birth weight (kg)	3.3 (IQR 2.9 - 3.6)

Female sex	17 (46%)
Class 1 (two ventricles, no aortic arch obstruction)	11 (30%)
Class 2 (two ventricles, aortic arch obstruction)	13 (35%)
Class 3 (single ventricle, no aortic arch obstruction)	2 (5%)
Class 4 (single ventricle, aortic arch obstruction)	11 (30%)
Age at start pre-operative monitoring (days)	4 (IQR 2 – 5)
Mechanical ventilation during pre-operative monitoring	9 (24%)
Continuous sedation during pre-operative monitoring	5 (14%)
CPB time (min)	166 (IQR 141 – 188)
Cross-clamp time (min)	92 (IQR 66 – 131)
Post-operative seizures	1 (3%)
Ventilator-free days	23 (IQR 19 – 25)
Post-operative ICU days	7 (IQR 6 – 10)
Mortality	3 (8%)

163 Abbreviations: CPB, cardiopulmonary bypass; ICU, intensive care unit; IQR, interquartile range.

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DISCUSSION

In this cohort of neonates with CHD requiring neonatal cardiac surgery and CBP, there was no difference in the mean absolute $crSO_2$ between the pre- and post-operative periods. However, there was a significant decrease in $crSO_2$ variability between the pre- and immediate post-operative period suggesting alterations in cerebral autoregulation which do not impact the absolute $crSO_2$ trends. Whether or not the duration and degree of post-operative $crSO_2$ variability impacts long-term neurodevelopmental outcomes remains unknown.

CBP allows surgeons to carry out intracardiac repairs of CHD by providing an alternate means of circulation and gaseous exchange without blood flowing into the heart or lungs. During CPB, deoxygenated blood returning to the heart is channeled to an extracorporeal oxygenator for gas exchange and subsequently returned via a cannula into the ascending aorta.[17] However, total cessation of circulation is necessary in some surgical repairs especially those requiring aortic arch reconstruction to allow for a bloodless surgical field. In such repairs, DHCA has traditionally been used to cool patients to a temperature range of 15 – 20˚C to reduce metabolic demands. [17] Newer techniques such as ACP allow maintenance of only cerebral perfusion during such complex repairs often shortening or eliminating of the need for DHCA.[17,18] Animal studies indicate that CPB leads to alterations in tissue oxygenation and hemoglobin parameters.[19,20] Our data suggest that alterations in cerebral autoregulation occur in the peri-operative period in neonates requiring surgery for CHD. The impact of these changes in unknown, but concerns remain that these alteration in cerebral autoregulation may adversely impact neurodevelopment in these patients. Future studies should include the investigation of additional intra-operative variables including anesthesia type as well as use of DHCA vs ACP.

An interesting finding in this study was the improvement in the pre-operative $crSO_2$ variability observed with each postnatal day prior to surgery in these neonates. Cerebral blood flow and hemodynamics are known to improve over time as neonates transition from fetal to extra-uterine circulation. Hence this a physiologically plausible finding. Considering the significant drop in $crSO_2$ variability after cardiac surgery, a robust variability prior to surgery may be desirable. Whether improved pre-operative $crSO_2$ variability is associated with improved neurodevelopmental outcomes and could be used to optimize surgery timing is unknown and should be further studied.

Our study has several limitations including its small and single center design. In addition, we were not able to include other vital sign parameters in our analysis. Future multicenter longitudinal studies exploring other important markers of perfusion such as mean arterial blood pressure variability, heart rate variability in addition to $crSO_2$ variability may further advance our understanding of the relationship between cerebral autoregulation and outcomes in neonates with CHD. Another limitation of this study is that two different NIRS monitors were utilized -the Foresight Elite® tissue oximeter (Edwards Lifesciences, Irvine, CA) pre-operatively and the INVOS™ 5100C® cerebral oximeter (Medtronic, Minneapolis, MN). Our measurement of interest - $CrSO_2$ variability is generally agnostic to the absolute value of the measured parameter.[3]

CONCLUSION

$crSO_2$ variability, which is a marker of cerebral autoregulation, decreases significantly in neonates with CHD after surgical repair involving CPB. Further research is needed to explore the long-term effects of this post-surgical drop in $crSO_2$ variability.

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AUTHOR CONTRIBUTIONS

M.O.A. made substantial contributions to the design, data acquisition and drafting of article.

M.C.S. made substantial contributions to the concept, design, data acquisition, analysis and interpretation of data and drafting of article.

S.A.Z. made substantial contributions to the data acquisition and review of draft and data interpretation.

ADDITIONAL INFORMATION

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Category of Study: Clinical Research

Patient Consent: Waived by the Institutional Review Board of the University Of Virginia School Of Medicine.

Figures

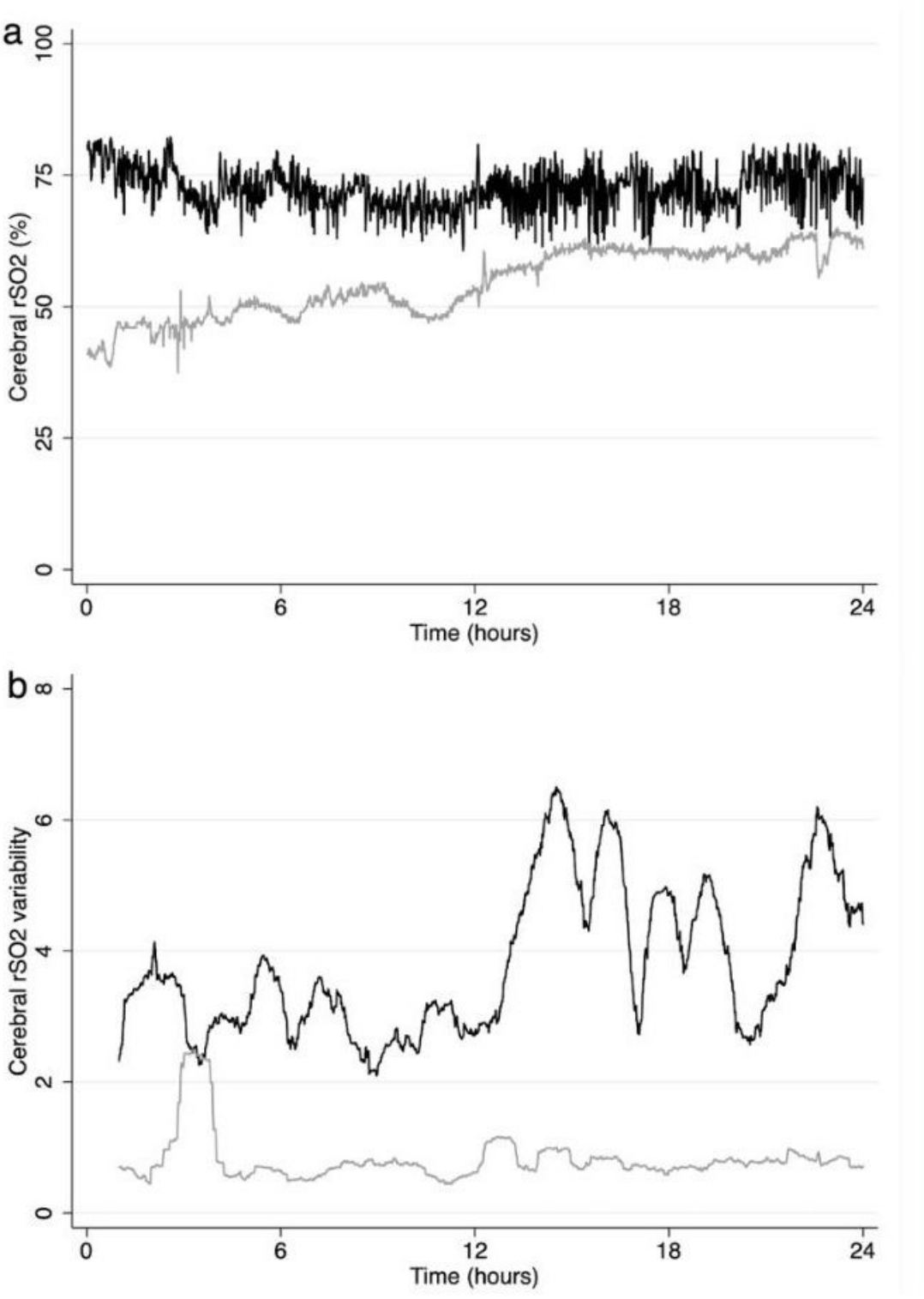

Figure 1

Time series plot of pre- and post-operative crSO2 values and corresponding crSO2 variability for a representative neonate.Time series plot of a crSO2 values and b crSO2 variability for patient with hypoplastic left heart syndrome captured pre- (black) and post- (grey) Norwood/Sano palliation.