



CLINICAL RESEARCH ARTICLE

Cerebral regional oxygen saturation variability in neonates following cardiac surgery

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BACKGROUND: Reduced cerebral regional oxygen saturation (crSO₂) variability in neonates, as measured by near-infrared spectroscopy, following cardiac surgery with deep hypothermic circulatory arrest (DHCA) is associated with poor neurodevelopmental outcomes. We sought to evaluate the variability of crSO₂ in a cohort of neonates following cardiac surgery with brief or no exposure to DHCA.

METHODS: Variability of averaged 1-min crSO₂ values was calculated for the first 48 h following cardiac surgery in consecutive neonates over a 30-month period. Neonates requiring aortic arch repair underwent antegrade cerebral perfusion with either brief or no exposure to DHCA.

RESULTS: There were 115 neonates included in the study. Reduced crSO₂ variability was observed in neonates with aortic arch obstruction ($p = 0.02$) and non-survivors ($p = 0.02$). Post hoc analysis demonstrated that the reduction in crSO₂ variability was not as marked as in previously studied neonates with aortic arch obstruction who received DHCA alone ($p < 0.001$).

CONCLUSIONS: Neonates with aortic arch obstruction have reduced crSO₂ variability following cardiac surgery. The reduction in crSO₂ variability observed in aortic arch obstruction is likely influenced by a number of factors, including perioperative perfusion technique. The impact of interventions on crSO₂ variability and resultant influence on neurodevelopmental outcomes requires further study.

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IMPACT:

- Neonates with aortic arch obstruction have reduced crSO₂ variability following cardiac surgery, which has been associated with poor neurodevelopmental outcomes, and is likely influenced by a number of factors, including perioperative perfusion technique.
- The contribution of perioperative perfusion technique to crSO₂ variability following neonatal cardiac surgery is significant.
- Monitoring of crSO₂ variability may provide insights into the adequacy of cerebral perfusion in neonates following cardiac surgery.

INTRODUCTION

Near-infrared spectroscopy (NIRS) is routinely used in the noninvasive monitoring of cerebral regional oxygen saturation (crSO₂) in neonates following surgery for congenital heart disease.^{1,2} Monitoring of crSO₂ can provide clinicians with insights into cerebral oxygen delivery and consumption in neonates following cardiac surgery.^{2–9}

Recent studies have demonstrated associations between crSO₂ values obtained following cardiac surgery in neonates and postoperative outcomes.^{10–12}

Measures of postoperative crSO₂ in published reports have typically involved the analyses of average crSO₂ values and indices of crSO₂ desaturation (e.g., period of time crSO₂ < 50% during first 24 h following surgery).^{10–14} More recently, studies have incorporated measures of crSO₂ variability into analyses similar to those employed in analyses of heart rate variability.^{12,13} In the neonatal literature, crSO₂ variability is reduced in premature neonates with

hypoxic-ischemic encephalopathy and those with exposure to chorioamnionitis.^{15,16}

Intracardiac repair is made possible by cardiopulmonary bypass (CPB), which takes over circulation and pulmonary gas exchange. The deoxygenated blood from the superior and inferior vena cavae is drained into a reservoir via a cannula and then passed through an oxygenator for gas exchange. The oxygenated blood is pumped back into the ascending aorta via another cannula. However, certain situations particularly where aortic arch reconstruction is performed mandate complete cessation of circulation.¹⁷ Historically, these situations have been overcome with deep hypothermic circulatory arrest (DHCA) whereby the patient is cooled (15–20 °C) and CPB flow is stopped, allowing for cannula removal and providing a bloodless and motionless surgical field.¹⁷ Antegrade cerebral perfusion is a newer technique that directs blood flow to only the brain during these complex stages of surgery, minimizing DHCA time or allowing for its avoidance altogether.^{17,18}

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Our group previously found that reduced crSO₂ variability in neonates following cardiac surgery with CPB and DHCA was associated with poor neurodevelopmental outcomes at 21 months of age.¹² In this study, we sought to evaluate the variability of crSO₂ in a cohort of neonates following cardiac surgery with brief or no exposure to DHCA.

METHODS

The Institutional Review Board at the University of Virginia School of Medicine approved this study. We included consecutive neonates (<30 days of age) that underwent cardiac surgery with CPB over a 30-month period from October 2017 to March 2020 at the University of Virginia Children’s Hospital. All patients underwent bi-caval venous cannulation and those patients requiring neonatal arch repair underwent antegrade cerebral perfusion (ACP) with either brief or no exposure to DHCA. All patients were monitored with continuous electroencephalography for the first 48 h following surgery.

Values of crSO₂ were continuously captured using the INVOS™ cerebral oximeter (Medtronic, Minneapolis, MN) over the first 48 h following surgery and averaged over 1-min intervals. Variability of crSO₂ was calculated using the root mean of successive squared differences (RMSSD) {1} of averaged 1-min crSO₂ values over the first 48 h following surgery:

$$RMSSD = \sqrt{\frac{\sum_{i=2}^n (x_i - x_{i-1})^2}{n}}$$
 (1)

where x_i is the crSO₂ at time i.

In more practical terms, the RMSSD measures the amount of change in crSO₂ from minute to minute over specified period of time. We imputed missing crSO₂ values by predictive mean matching. To characterize changes in crSO₂ variability over time, we also calculated a 60-min moving variability measure for each minute of monitoring using the RMSSD from the previous 60 min.¹²

Patient and clinical characteristics, including age at the time of surgery, CPB and cross-clamp times, cardiac diagnosis, surgical procedure, and postoperative ventilator and intensive care unit days, were collected. Patients were assigned to one of four previously described diagnostic classes: class 1—two ventricle repair without aortic arch obstruction, class 2—two ventricle repair with aortic arch obstruction, class 3—single ventricle repair without aortic arch obstruction, or class 4—single ventricle repair with aortic arch obstruction.¹⁹

In a post hoc analysis, we compared the crSO₂ variability of neonates with aortic arch obstruction (classes 2 and 4) in our cohort with those from our previously published study who all underwent DHCA.¹² As our previous study was limited to monitoring for the first 24 h following surgery, we used the crSO₂ variability at 24 h in the present study for the comparison.

Distribution of continuous variables was assessed using the Wilk–Shapiro test for normality. Continuous variables were compared using Student’s t test, Wilcoxon’s rank-sum testing, or linear regression as appropriate. Categorical variables were compared using χ² test or Fisher’s exact testing 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

There were 115 neonates included in the study with a median of 8 days of age (interquartile range (IQR) 5–10 days) at the time of surgery. The demographic and clinical characteristics of the included patients are listed in Table 1.

Table 1. Patient demographic and clinical characteristics.

Characteristic	n (%)
Age (days)	8 (IQR 5–10)
Female sex	42 (37%)
Class 1 (two ventricles, no aortic arch obstruction)	41 (36%)
Class 2 (two ventricles, aortic arch obstruction)	37 (33%)
Class 3 (single ventricle, no aortic arch obstruction)	6 (5%)
Class 4 (single ventricle, aortic arch obstruction)	30 (26%)
CPB time (min)	185 (IQR 157–215)
Cross-clamp time (min)	113 (IQR 82–143)
Postoperative seizures	3 (3%)
Postoperative ventilator days	4 (IQR 3–6)
Postoperative ICU days	7 (IQR 6–13)
Mortality	5 (4%)

CPB cardiopulmonary bypass, ICU intensive care unit, IQR interquartile range.

Variability of crSO₂ was not associated with patient age, single ventricle repair, durations of CPB or cross-clamp, and post-operative seizures, ventilator, or intensive care unit days. Patients with aortic arch obstruction (p = 0.02) and non-survivors (p = 0.02) demonstrated reduced crSO₂ variability during the first 48 h following surgery. The time-series plots of crSO₂ values and corresponding crSO₂ variability of two representative neonates are shown in Fig. 1.

All patients with aortic arch obstruction underwent ACP with a median duration of 43 min (IQR 29–84 min). Thirty-four (52%) of these patients underwent brief DHCA with a median duration of 7 min (IQR 4–12 min). Neither duration of antegrade cerebral perfusion or DHCA was associated with crSO₂ variability. We stratified clinical characteristics and outcomes by aortic arch obstruction in Table 2.

To compare the 67 patients with aortic arch obstruction from this cohort with patients with aortic arch obstruction from our previous DHCA cohort, we calculated the crSO₂ variability reflective of the first 24 h following surgery. The median crSO₂ variability over the first 24 h was 1.4 (IQR 1.2–1.8), not different from the crSO₂ variability for the entire 48-h period of monitoring (p = 0.09). In our previous study, there were 41 patients with aortic arch obstruction with a median duration of DHCA of 46 min (IQR 38–51 min) and crSO₂ variability of 1 (IQR 0.8–1.4).¹² The patients from our previous DHCA cohort were younger at the time of surgery (4 vs. 6 days, p < 0.001) and more likely to undergo single ventricle repair (p < 0.001). There was no difference in the minimum temperature achieved during cooling between the groups (18 °C in both groups). When comparing the cohorts, patients with aortic arch obstruction who received antegrade cerebral perfusion had 40% greater crSO₂ variability at 24 h following surgery (1.4 vs. 1, p < 0.001).

DISCUSSION

We observed reduced crSO₂ variability in neonates with aortic arch obstruction in the first 48 h following cardiac surgery with antegrade cerebral perfusion and brief or no exposure to DHCA. The reduction in crSO₂ variability was not as marked as in previously studied neonates who received DHCA alone. The reduction in crSO₂ variability observed in aortic arch obstruction is likely influenced by a number of factors.

Brain-sparing refers to the adaptation of autoregulatory mechanisms to increase cerebral perfusion in fetuses with congenital heart

disease.²⁰ Fetal ultrasound studies have demonstrated that fetuses with hypoplastic left heart syndrome may have inadequate autoregulatory compensatory mechanisms, influencing neurodevelopmental abnormalities observed in this group.^{20–22} Fetuses with aortic arch obstruction have decreased middle cerebral artery pulsatility indices, indicating restricted cerebral blood flow in this group.²³ During the transition to extrauterine life there is a decline in

pulmonary vascular resistance and increase in system vascular resistance. In the neonate with ductal-dependent cardiac lesions, the maintenance of adequate cerebral blood flow in the setting of decreased pulmonary vascular resistance and an open ductus arteriosus may be difficult.²⁴ There is evidence to suggest a persistence of impaired cerebral autoregulation in neonates with congenital heart disease during the first 24–48 h of life prior to cardiac surgery.^{24,25} The degree to which fetal and transitional cerebral autoregulation and perfusion impacts crSO₂ variability in the early neonatal period requires further study.

The impact of the type of perfusion technique employed during neonatal cardiac surgery on neurodevelopmental outcomes remains controversial.²⁶ The findings of the Boston Circulatory Arrest Trial suggest that a duration of DHCA of 41 min or less does not adversely impact neurodevelopmental outcomes as measured at 8 years of age.²⁷ Two studies have demonstrated no difference in neurodevelopmental outcomes at 1 year of age in infants who underwent aortic arch reconstruction between DHCA alone and DHCA with brief or no antegrade cerebral perfusion.^{28,29} More recently, in a cohort of neonates receiving antegrade cerebral perfusion undergoing aortic arch reconstruction with specialized intraoperative neuromonitoring, Andropoulos et al.³⁰ demonstrated 12-month cognitive outcomes at reference population norms.

In our previous work, we found an association between decreased crSO₂ variability and worse neurodevelopmental outcomes at 21 months of age.¹² We observed a strong association between duration of DHCA and degree of crSO₂ variability reduction (i.e., longer DHCA duration associated with a greater reduction of crSO₂ variability).¹² Our observation in the present study of reduced crSO₂ variability in neonates with aortic arch obstruction, although with significantly less reduction than in our previous study, supports the notion that multiple factors (e.g., intrauterine, transitional, perioperative) influence our findings.

There are several limitations to our study, including the single-center nature. We are limited in our ability to make conclusions regarding the impact of therapeutic interventions on crSO₂ variability, although our institutional practice is largely uniform as it relates to the selection and use of sedative and vasoactive infusions in the postoperative period. Conclusions drawn from our comparison of data from the present study with our previous study require careful consideration given a number of limitations. While both cohorts were limited to patients with aortic arch obstruction, the patients in the previous cohort were younger (4 vs. 6 days) and more likely to undergo single ventricle repair. In addition, our prior study employed a different NIRS monitor (NIRO-200; Hamamatsu Photonics KK, Hamamatsu, Japan).¹² Studies have demonstrated differences in the absolute values of regional oxygen saturation indices between different NIRS monitors.^{5,31} However, the calculation of variability is, by definition, agnostic to

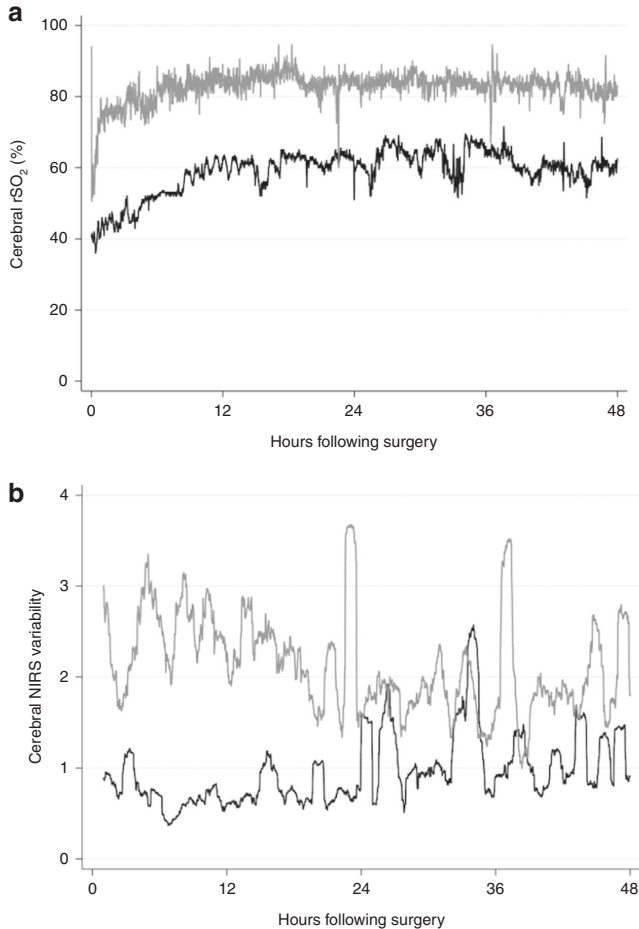


Fig. 1 Time-series plot of crSO₂ values and corresponding crSO₂ variability of two representative neonates. Time-series plot of **a** crSO₂ values and **b** crSO₂ variability for patient with *d*-transposition of the great arteries s/p arterial switch operation (gray) and patient with hypoplastic left heart syndrome s/p Norwood/Sano palliation (black).

Table 2. Clinical characteristics and outcomes stratified by the presence or absence of aortic arch obstruction.

Characteristic	Aortic arch obstruction (n = 67)	No aortic arch obstruction (n = 48)	P value
Age (days)	6 (IQR 5–10)	8 (IQR 7–13)	0.03
Single ventricle repair	30 (45%)	6 (13%)	<0.001
CPB time (min)	187 (IQR 156–224)	185 (IQR 156–212)	0.62
Cross-clamp time (min)	97 (IQR 80–125)	139 (IQR 97–154)	0.002
Postoperative ventilator days	5 (IQR 3–8)	3 (IQR 3–5)	0.01
Postoperative ICU days	10 (IQR 6–15)	6 (IQR 5–9)	<0.001
Mortality	3 (4%)	2 (4%)	0.66
Average crSO ₂ (%)	71 (SD 9)	75 (SD 7)	0.01
crSO ₂ variability	1.5 (IQR 1.3–1.8)	1.7 (IQR 1.5–1.9)	0.02

crSO₂ cerebral regional oxygen saturation, ICU intensive care unit, IQR interquartile range, SD standard deviation.

the measured index so the comparison of values between devices should not be significantly impacted.

There are some important next steps to consider. First, at present, we are not aware of a commercially available NIRS device that provides readily accessible $crSO_2$ variability data. As such, monitoring of $crSO_2$ variability requires the extraction of $crSO_2$ values from the NIRS device for the extra-device calculation and assessment of variability. The integration of variability measures with NIRS devices could potentially enhance the value of these measures for real-time clinical assessment and decision support. Second, we have recently initiated work on a follow-up project, capturing both preoperative and postoperative values in neonates undergoing cardiac surgery, in an effort to better understand the perioperative influence on crO_2 variability. Finally, assessing the relationship between $crSO_2$ variability and neurodevelopmental outcomes in patients with minimal or no exposure to DHCA will be an important next step.

Neonates with aortic arch obstruction have reduced $crSO_2$ variability following cardiac surgery. The reduction in $crSO_2$ variability observed in aortic arch obstruction is likely influenced by a number of factors, including perioperative perfusion technique. The impact of interventions on $crSO_2$ variability and resultant influence on neurodevelopmental outcomes requires further study.

AUTHOR CONTRIBUTIONS

M.C.S. made substantial contributions to the conception and design, acquisition, analysis and interpretation of data; drafted the article for important intellectual content; and approved the final version to be published. V.J.S. made substantial contributions to the acquisition of data; and approved the final version to be published.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

Statement of ethics: The authors received a waiver of consent by the Institutional Review Board at the University of Virginia School of Medicine for this study.

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