Perioperative Near-Infrared Spectroscopy Monitoring in Neonates With Congenital Heart Disease: Relationship of Cerebral Tissue Oxygenation Index Variability With Neurodevelopmental Outcome

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Objectives: To evaluate the value of perioperative cerebral near-infrared spectroscopy monitoring using variability analysis in the prediction of neurodevelopmental outcomes in neonates undergoing surgery for congenital heart disease.

Design: Retrospective cohort study.

Setting: Urban, academic, tertiary-care children's hospital.

Patients: Neonates undergoing surgery with cardiopulmonary bypass for congenital heart disease.

Interventions: Perioperative monitoring of continuous cerebral tissue oxygenation index by near-infrared spectroscopy and subsequent neurodevelopmental testing at 6, 15, and 21 months of age.

Measurements and Main Results: We developed a new measure, cerebral tissue oxygenation index variability, using the root mean of successive squared differences of averaged 1-minute cerebral tissue oxygenation index values for both the intraoperative and first 24-hours postoperative phases of monitoring. There were 62 neonates who underwent cerebral tissue oxygenation index monitoring during surgery for congenital heart disease and 44 underwent subsequent neurodevelopmental testing (12 did not survive until testing and six were lost to follow-up). Among the 44 monitored patients who underwent neurodevelopmental testing, 20 (45%) had abnormal neurodevelopmental indices. Patients with abnormal neurodevelopmental indices had lower postoperative cerebral tissue oxygenation index variability when compared with patients with normal indices ($p = 0.01$). Adjusting for class of congenital heart disease and duration of deep hypothermic circulatory arrest, lower postoperative cerebral tissue oxygenation index variability was associated with poor neurodevelopmental outcome ($p = 0.02$).

Conclusions: We found reduced postoperative cerebral tissue oxygenation index variability in neonatal survivors of congenital heart disease surgery with poor neurodevelopmental outcomes. We hypothesize that reduced cerebral tissue oxygenation index variability may be a surrogate for impaired cerebral metabolic autoregulation in the immediate postoperative period. Further research is needed to investigate clinical implications of this finding and opportunities for using this measure to drive therapeutic interventions. (*Pediatr Crit Care Med* 2017; 18:213–218)

Key Words: congenital heart defects; infant; near-infrared spectroscopy; neurodevelopmental disorders; physiologic monitoring

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Near-infrared spectroscopy (NIRS) is routinely used for noninvasive monitoring of cerebral tissue oxygenation in infants undergoing surgery for congenital heart disease (CHD) (1–6). Despite the increasing acceptance of NIRS monitoring as standard practice in pediatric cardiac anesthesia and cardiac ICU (CICU), considerable variability continues to exist in the role monitoring plays in clinical decision-making and patient outcome (7).

The most common complication for survivors of surgery for CHD is neurodevelopmental disability (8). Although there are some data supporting the use of NIRS to predict outcome in CHD infants undergoing cardiopulmonary bypass (CPB), there are limited data demonstrating a clear relationship between perioperative cerebral tissue oxygenation measured by NIRS and neurodevelopmental outcome in survivors.

The typical approach in the published literature involves analysis of the average, maximum, and nadir regional oxygen saturation (rSO_2) or cerebral tissue oxygenation index (cTOI) values, often partitioned by the various phases of intraoperative and postoperative courses (1–4). This includes a study performed at our institution, which showed that postoperative NIRS data combined with lactate were able to predict poor outcome defined as poor neurodevelopmental outcome or death (9). Given the duration and complexity of the multiphasic perioperative course of surgery for CHD, we hypothesize that alternative analytic approaches may better characterize the behavior of rSO_2 or cTOI over time in neonates undergoing bypass surgery.

It has been observed that adults and children with sepsis and septic shock exhibit reduced beat-to-beat variability of heart rate, suggesting an uncoupling of the autonomic and cardiovascular systems on a physiologic level (10–12). Extending this observation to regional tissue oxygenation, we surmised that reduced variability might signify impaired autoregulation or inadequacy of compensatory mechanisms. Using this as our hypothesis, we demonstrated in a retrospective analysis reduced variability of abdominal rSO_2 in the hour preceding diagnosis of low cardiac output syndrome in a cohort of neonates who underwent surgery for repair of CHD (13). We hypothesize that cTOI variability measured by continuous NIRS monitoring in the intraoperative and postoperative period is predictive of neurodevelopmental outcomes in surviving neonates undergoing surgery for CHD.

MATERIALS AND METHODS

The Institutional Review Board at the Children's National Health System approved this study. We performed a secondary analysis of prospectively collected cTOI values in neonates less than 6 weeks of age undergoing surgery for CHD from 2006 to 2012 (9). We excluded neonates who did not require CPB during surgery. The analysis was performed in the survivors given that neurodevelopmental outcome before 2 years old was our endpoint.

A pediatric cerebral NIRS probe (NIRO-200; Hamamatsu Photonics KK, Hamamatsu, Japan) was placed in the operating room at the beginning of the intraoperative course and remained for at least the first 24 hours following surgery. cTOI values were collected every 1 second and displayed continuously in an unblinded fashion. For each patient, there was a short time interval following surgery during transport from the operating room to the CICU that cTOI values were unable to be collected.

For each patient, per second cTOI values were averaged over 1-minute time intervals and plotted as a time series. The mean, median, and nadir cTOI values were calculated for both phases (intraoperative and postoperative) of monitoring.

cTOI variability was calculated using the root mean of successive squared differences (RMSSD) [*1*] for both phases of monitoring (14, 15).

$$\mathrm{RMSSD} = \sqrt{\frac{\sum_{i=2}^{n}\left(x_i - x_{i-1}\right)^2}{n}}, \quad (1)$$

where x_i is the cTOI at time i. In more practical terms, the RMSSD measures the amount of change in cTOI from minute to minute over the course of a specified time period. In our case, we calculated one measure for the intraoperative phase and one measure for the postoperative phase for each patient. Furthermore, to characterize changes in cTOI variability over time, we also calculated a 60-minute moving variability measure for each minute of monitoring using the RMSSD from the preceding 60 minutes.

Patient and clinical characteristics including age at time of surgery, CICU admission weight and CPB times were collected. Patients were assigned to one of four previously described diagnostic classes by the study cardiologists (D. K., M. T. D.): class 1—two ventricle repair without aortic obstruction, class 2—two ventricle repair with aortic obstruction, class 3—single ventricle repair without aortic obstruction, or class 4—single ventricle repair with aortic obstruction (16). Neuroimaging interpretations by a pediatric diagnostic radiologist or neuroradiologist of pre- and postoperative studies (MRI and cranial ultrasound) were reviewed in the cohort of patients for whom they were performed.

Neurodevelopmental outcomes were assessed in survivors at 6, 15, and 21 months following surgery using the Bayley Scales of Infant Development II Psychomotor Development Index (PDI) and Mental Development Index (MDI) (17). Poor outcome was defined as a PDI or MDI score of less than 70 at 21 months of age compared with normative means. In the event that a patient did not present for assessment at 21 months of age, previous assessment results were used to establish outcome with preference toward the assessment at 15 months of age.

Distribution of continuous variables was assessed using the Wilk-Shapiro test for normality and measures of central tendency are presented as either means and SD or medians and interquartile ranges (IQRs) as appropriate. Continuous variables were compared using Student *t* test, Wilcoxon signed rank test, or Spearman rank correlation test as appropriate. Categorical variables were compared using chi-square test or Fisher exact test as appropriate. Multivariable logistic regression was performed to adjust for confounders. We created receiver operating characteristic (ROC) curves to assess the ability of variables to discriminate clinical outcome. Type I error was set at 0.05. All calculations were performed using STATA/IC 12.1 (College Station, TX).

RESULTS

There were 62 neonates who underwent cardiac repair or palliation using CPB monitored during the period of study. The mean age of patients at time of surgery was 8 days (SD, 8.5 d) and mean weight on CICU admission was 3,289 g (SD, 550 g). Patients were classified on the basis of their CHD diagnosis (**Table 1**). Thirty-six patients (58%) had single ventricle repair

TABLE 1. Classification of Monitored Patients by Congenital Heart Disease Diagnosis

Classification	Frequency by Diagnosis ($n = 62$)
Class 1 ($n = 21$) Two ventricles, no aortic obstruction	d-TGA/intact ventricular septum ($n = 10$) d-TGA/VSD ($n = 4$) Total anomalous pulmonary venous return ($n = 2$) Double outlet right ventricle ($n = 2$) Truncus arteriosus ($n = 1$) Tetralogy of Fallot ($n = 1$) VSD ($n = 1$)
Class 2 ($n = 5$) Two ventricles, aortic obstruction	VSD with coarctation of aorta ($n = 4$) VSD with hypoplastic aortic arch ($n = 1$)
Class 3 ($n = 0$) Single ventricle, no aortic obstruction	
Class 4 ($n = 36$) Single ventricle, aortic obstruction	Hypoplastic left heart syndrome ($n = 25$) Other single ventricle defects with aortic obstruction ($n = 11$)

d-TGA = d-transposition of the great arteries, VSD = ventricular septal defect.

(class 3 and 4) and 41 patients (66%) had aortic obstruction (class 2 and 4).

Twelve patients (19%) did not survive to neurodevelopmental testing and six patients (10%) were lost to follow up. Nonsurvivors had lower CICU admission weight (2,822 vs 3,400 g; $p < 0.001$). There were no differences in age, CPB time, or distribution of heart disease diagnosis between survivors and nonsurvivors. Patients lost to follow up had longer CPB times (145 vs 120 min; $p = 0.045$). There were no differences in age, CICU admission weight, or distribution of heart disease diagnosis between patients lost to follow up and patients who underwent neurodevelopmental testing.

Among the 44 monitored patients who underwent neurodevelopmental testing, 20 (45%) had abnormal neurodevelopmental indices—nine patients (20%) had both abnormal PDI and MDI, seven patients (16%) had abnormal PDI alone, and four (9%) had abnormal MDI alone. Patient and clinical characteristics were compared based on neurodevelopmental outcome (**Table 2**). There were no differences in age, weight, CPB time, mean, or nadir cTOI in either phase between the groups. Longer duration of deep hypothermic circulatory arrest (DHCA), single ventricle repair (class 3 and 4), and aortic obstruction (class 2 and 4) were all associated with poor neurodevelopmental outcome ($p = 0.01$, 0.03, and 0.04, respectively).

Postoperative cTOI variability was lower in patients with poor neurodevelopmental outcomes (RMSSD = 1 [IQR, 0.8–1.7] vs 1.6 [IQR, 1.2–3]; $p = 0.01$). Separating poor neurodevelopmental outcome into each of its components, postoperative cTOI variability was lower in both patients with poor PDI (RMSSD = 0.9 [IQR, 0.8–1.6] vs 1.6 [IQR, 1.1–2.6]; $p = 0.02$) and poor MDI (RMSSD = 0.9 [IQR, 0.8–1] vs 1.6 [IQR, 1.2–3]; $p = 0.003$). There was no difference in postoperative cTOI variability in nonsurvivors (RMSSD = 1.2 [IQR, 0.8–2.3]) when compared with survivors, in general, or stratified by neurodevelopmental outcome. There was no difference in intraoperative cTOI variability based on neurodevelopmental outcome.

Patients with single ventricle repair (class 3 and 4) had lower postoperative cTOI variability when compared with patients with two ventricles (RMSSD = 1 [IQR, 0.8–1.3] vs 2 [IQR, 1.6–3]; $p < 0.001$). Patients with aortic obstruction (class 2 and 4) had lower postoperative cTOI variability when compared with patients without aortic obstruction (RMSSD = 1 [IQR, 0.8–1.4] vs 2 [IQR, 1.6–3]; $p < 0.001$). DHCA duration was negatively correlated with postoperative cTOI variability ($r = -0.3730$; $p = 0.015$).

Adjusting for CHD class and duration of DHCA, lower postoperative cTOI variability was associated with poor neurodevelopmental outcome ($p = 0.02$). Separating poor neurodevelopmental outcome into each of its components, after adjusting for single CHD class and duration of DHCA, lower postoperative cTOI variability was associated with both poor MDI ($p = 0.01$) and poor PDI ($p = 0.03$).

We performed ROC curve analyses on the ability of postoperative cTOI variability to discriminate neurodevelopmental outcome. The ability of postoperative cTOI variability to discriminate neurodevelopmental outcomes in general, and PDI in particular, was fair (area under the curve [AUC] = 0.7198 and 0.7121, respectively). The ability of postoperative cTOI variability to discriminate MDI was good (AUC = 0.7903) (**Fig. 1**). A postoperative cTOI variability of less than 1.05 best predicted poor MDI with 87% sensitivity and 77% specificity.

To illustrate the behavior of postoperative cTOI variability over time, we plotted the average cTOI 60-minute moving variability stratified by neurodevelopmental outcome (**Fig. 2**). Similar to postoperative cTOI variability, patients with poor neurodevelopmental outcome had lower average cTOI 60-minute moving variability when compared with patients with good neurodevelopmental outcome (0.9 vs 1.6; $p < 0.001$).

Twenty-one patients (47%) underwent preoperative neuroimaging (15 MRI, six cranial ultrasound) with five patients reported to have abnormal studies. Fourteen patients (32%) underwent postoperative neuroimaging (11 MRI, three cranial ultrasound) including 10 patients who had also undergone preoperative neuroimaging and a total of four patients reported to have abnormal studies. In the cohort of patients that underwent neuroimaging studies, there was no relationship between the presence of abnormal findings (e.g., intracranial bleeding, white matter injury) and postoperative cTOI variability or neurodevelopmental outcome.

TABLE 2. Patient and Clinical Characteristics Stratified by Neurodevelopmental Outcome

Characteristic	Normal Neurodevelopmental Outcome (*n* = 24) *n* (%)	Poor Neurodevelopmental Outcome (*n* = 20) *n* (%)	*p*
Age (d)	6 (IQR, 3–7)	6 (IQR, 4–9)	0.27
Weight (g)	3,482 (SD, 475)	3,320 (SD, 495)	0.14
Cardiopulmonary bypass time (min)	123 (IQR, 109–143)	116 (IQR, 106–125)	0.36
Underwent DHCA	24 (100%)	18 (90%)	0.20
DHCA time (min)	25 (IQR, 8–42)	45 (IQR, 39–50)	**0.01**
CHD classification			0.06
Class 1	12 (50%)	4 (20%)	
Class 2	2 (8%)	1 (5%)	
Class 3	0	0	
Class 4	10 (42%)	15 (75%)	
Single ventricle defects (class 3 and 4)	10 (42%)	15 (80%)	**0.03**
CHD with aortic obstruction (class 2 and 4)	12 (50%)	16 (80%)	**0.04**
Mean intraoperative cTOI	63 (SD, 7)	63 (SD, 9)	0.41
Nadir intraoperative cTOI	35 (SD, 14)	33 (SD, 16)	0.31
Intraoperative cTOI variability	2.7 (IQR, 2.2–3.5)	2.7 (IQR, 2.1–3.9)	0.99
Mean postoperative cTOI	56 (SD, 12)	55 (SD, 11)	0.32
Nadir postoperative cTOI	34 (SD, 16)	38 (SD, 11)	0.71
Postoperative cTOI variability	1.6 (IQR, 1.2–3)	1 (IQR, 0.8–1.7)	**0.01**

cTOI = cerebral tissue oxygenation index, CHD = congenital heart disease, DHCA = deep hypothermic circulatory arrest, IQR = interquartile range.
Boldface values reflect significant results.

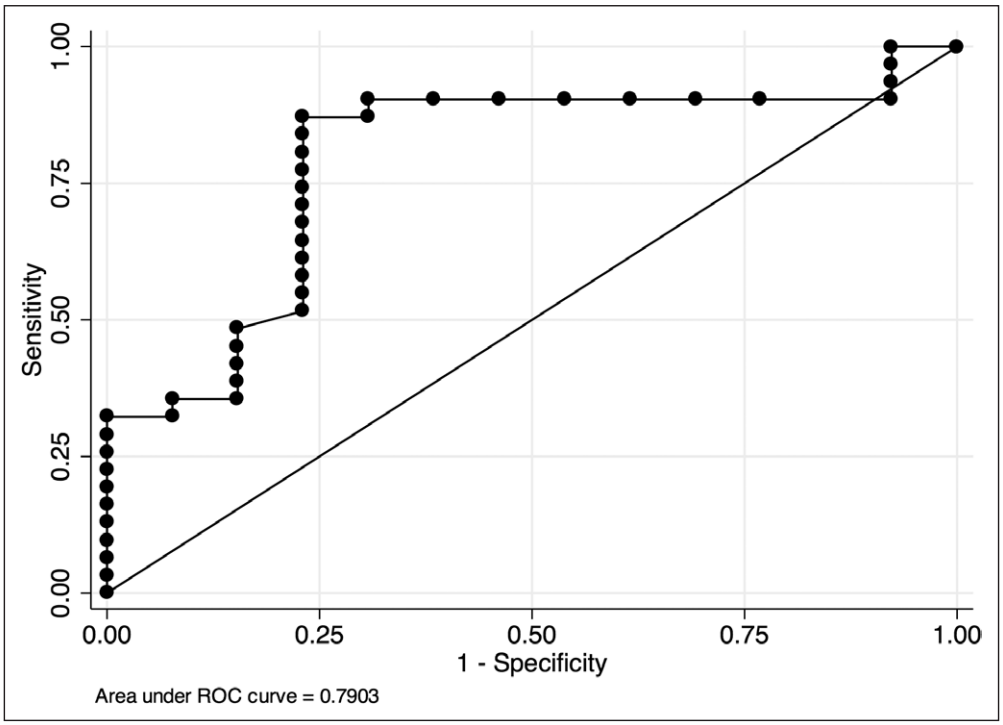

Figure 1. Discrimination of Bayley scales of infant development II mental development index by postoperative cerebral tissue oxygenation index variability. ROC = receiver operating characteristic.

DISCUSSION

Our results suggest that reduced variability of cTOI in the initial postoperative period following CPB for CHD surgery in neonates is associated with poor neurodevelopmental outcome even after adjusting for known confounders such as single ventricle repair, aortic obstruction, and duration of DHCA.

Clinical Implications

Variability of cTOI was reduced in patients undergoing single ventricle repair and with aortic obstruction and was negatively correlated with duration of DHCA. Not surprisingly, patients who either had single ventricle repair and/or aortic obstruction had longer durations of DHCA. Among the patients in our study

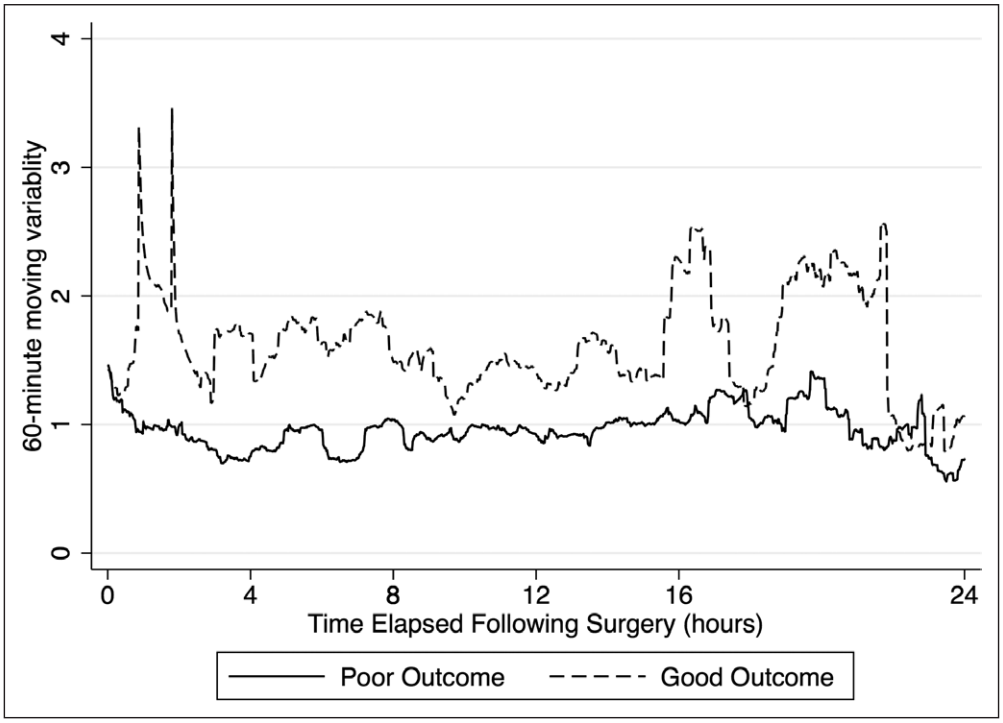

Figure 2. Comparison of postoperative cerebral tissue oxygen index 60-min moving variability based on neurodevelopmental outcome.

with poor neurodevelopmental outcomes, the median duration of DHCA was 45 minutes, close to range generally accepted as the threshold beyond which risk of poor outcome is increased (18).

The inverse relationship between cTOI variability and DHCA duration suggests that reduced cTOI variability may be a surrogate for impaired cerebral metabolic autoregulation in the immediate postoperative period. Acceptance of this hypothesis would require sufficient evidence that cTOI variability increases over time following DHCA as cerebral metabolic autoregulation normalizes. As illustrated in Figure 2, the 60-minute moving variability among the patients with poor neurodevelopmental outcome did not change significantly over the course of the first 24 hours following surgery. As such, our study is limited by the duration of postoperative monitoring and subsequent efforts should be made to investigate this hypothesis formally.

Technical Considerations

By employing the Beer-Lambert law, NIRS allows for noninvasive indirect monitoring of tissue oxygenation and hemoglobin content and provides a surrogate for fluctuations in cerebral blood flow (19, 20). Depending on the device manufacturer, the NIRS monitor provides one of two different indices (cTOI or rSO_2) though both are expressed as percentages of oxygenated hemoglobin relative to total hemoglobin (21). Both indices demonstrate significant correlation with central venous oxygen saturation in infants and children (22, 23).

There are important differences between the devices, including the algorithms employed to calculate the indices. Studies comparing rSO_2 and cTOI in both animal and human subjects demonstrate differences in the absolute values of the indices with mean rSO_2 typically higher than mean cTOI (21, 22). Calculation of variability is, by definition, agnostic to the absolute value of the measured index. As such, while only our subjects' cTOI was monitored, it is reasonable to postulate that similar results might have been observed had we simultaneously monitored rSO_2 in our cohort, although this certainly warrants further study.

Limitations

Limitations of our work include the single-center, retrospective nature of the study. As discussed above, nearly our entire cohort underwent DHCA and so we cannot comment on the value of cTOI variability in patients undergoing regional cerebral perfusion. Although it has been demonstrated in infants undergoing single ventricle repair randomized to regional cerebral perfusion or DHCA that there are no differences in neurodevelopmental outcomes, further study is needed to differentiate cTOI variability between these two strategies (24). The use of neuroimaging modalities, either to evaluate potential associations with cTOI variability or neurodevelopmental outcome, was not uniform among our cohort and thus needs to be better evaluated in future studies. Advanced neuroimaging techniques, such as MRI with diffusion tensor imaging and magnetic resonance spectroscopy, which can detect microstructural and metabolic abnormalities, may prove more valuable in detecting a potential association with cTOI variability. Finally, we are limited in our ability to make any conclusions regarding the impact of therapeutic intervention on cTOI variability, which should be the focus of future investigation.

CONCLUSIONS

We found reduced postoperative cTOI variability in neonatal survivors of CHD surgery with poor neurodevelopmental outcomes. Further research is needed to investigate clinical implications of this finding and opportunities for using this measure to drive therapeutic interventions.

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