Predictive value of perioperative near-infrared spectroscopy for neurodevelopmental outcomes after cardiac surgery in infancy

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Objective: The study objective was to expand on prior research examining intraoperative regional cerebral oxygen saturation (rSO₂) measured by near-infrared spectroscopy (NIRS) by evaluating the predictive value of perioperative NIRS monitoring for neurodevelopmental outcomes after infant cardiac surgery.

Methods: Cross-sectional neurodevelopmental evaluation at 24 months of age with the Bayley Scales of Infant and Toddler Development, Third Edition was performed for patients who underwent cardiac surgery with perioperative NIRS monitoring between 2007 and 2010. Retrospective clinical data were extracted from the electronic medical record. Evaluation of selected NIRS measures, including preoperative rSO₂ (baseline) as well as rSO₂ nadir and percent decrease from baseline during the intraoperative and early postoperative periods, was undertaken.

Results: Perioperative NIRS and neurodevelopmental data were available for 31 patients without chromosomal anomalies who underwent cardiac surgery during infancy at a median age of 0.43 months. Optimal thresholds on NIRS measures identified through receiver operating characteristic analyses were intraoperative percent decrease of 52% for receptive communication delay and postoperative rSO₂ nadir of 56% for cognitive delay and 49% for gross motor delay. When considered in conjunction with other clinical characteristics in stepwise linear regression analyses, intraoperative percent decrease of more than 52% entered into the final model for receptive communication outcome and postoperative rSO₂ nadir of less than 56% entered into the final model for cognitive outcome.

Conclusions: Perioperative NIRS monitoring seems to enhance the ability to predict neurodevelopmental outcome. Specific NIRS measures associated with neurodevelopmental outcome, as well as optimal thresholds, seem to differ across the continuum of the perioperative period. (J Thorac Cardiovasc Surg 2013;145:438-45)

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With the dramatic decline in mortality for children with congenital heart disease (CHD), attention has been directed toward functional outcomes. Neurodevelopmental (ND) impairment is the most common morbidity affecting the quality of life of children with CHD who required surgical intervention.¹ Perioperative regional cerebral oxygen

saturation (rSO₂) has been identified as a potential contributor to ND outcomes in this population^{2,3}; as a result, monitoring rSO₂ with near-infrared spectroscopy (NIRS), a noninvasive optical technique that monitors brain tissue oxygen saturation through measurement of oxyhemoglobin and de-oxyhemoglobin concentrations, is gaining acceptance.⁴⁻⁶ However, a body of research correlating NIRS data with ND scores and showing that these data can be used to improve outcomes is needed before the value of routine NIRS monitoring for pediatric cardiac surgery can be determined.^{7,8}

The few published studies that have examined the relationship between rSO₂ measured by NIRS and ND outcomes have focused exclusively on the preoperative or intraoperative (IO) periods.⁹⁻¹¹ Despite extensive research documenting decreased oxygen delivery during the early postoperative (PO) period¹²⁻¹⁵ and an association between PO events (eg, seizures, cardiac arrest, circulatory instability) and neurologic or ND outcomes,¹⁶⁻¹⁸ there are no published data examining the relationships between PO NIRS measures and neurodevelopment. Without these data, the predictive and clinical utility of this tool during the perioperative period are unknown. This study seeks to expand on our previous work on the assessment of IO

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Abbreviations and Acronyms

AUC	= area under the curve
CHD	= congenital heart disease
CPB	= cardiopulmonary bypass
DHCA	= deep hypothermic circulatory arrest
IO	= intraoperative
ND	= neurodevelopmental
NIRS	= near-infrared spectroscopy
NPV	= negative predictive value
PO	= postoperative
PPV	= positive predictive value
ROC	= receiver operating characteristic
rSO ₂	= regional cerebral oxygen saturation

rSO₂ by evaluating the predictive value of selected NIRS measures across the continuum of the perioperative period for ND outcome at 24 months of age.

MATERIALS AND METHODS

Participants and Study Design

Participants were a subset (N = 31) of 62 patients enrolled across 2 cross-sectional, retrospective research studies examining ND outcome at 24 months of age after infant cardiac surgery.^{11,19} The Nemours Institutional Review Board approved both studies, and parental permission was obtained from the parents/legal guardians before participation. Among 44 patients without a chromosomal anomaly, 31 had perioperative NIRS data available for the first (N = 29) or second (N = 2) surgery with cardiopulmonary bypass (CPB) between 2007 and 2010. All patients were aged less than 12 months at the time of surgery and were aged 24 ± 3 months at the time of the ND assessment.

Operative Management

Patients were managed preoperatively and postoperatively in a dedicated cardiac intensive care unit. Operative management has been described.¹¹ Perioperative management decisions were not made on the basis of NIRS data. The majority of patients in this sample had deep hypothermic circulatory arrest (DHCA) (94%), because this was an inclusion criterion for one of the larger studies. Total body intermittent perfusion was performed when a period of DHCA greater than 40 minutes was anticipated.

Near-Infrared Spectroscopy

Recording of rSO₂ with NIRS (INVOS 5100B; INVOS 5100C; Somatronics, Troy, Mich) was undertaken before, during, and up to 48 hours after congenital cardiac surgery by placement of a probe on the forehead in the midline position. The first NIRS value after induction of anesthesia was considered the baseline rSO₂. NIRS readings during the IO and early PO periods were used to calculate the lowest rSO₂ (rSO₂ nadir) and percent decrease from baseline rSO₂ (percent decrease) across the continuum of the perioperative period and separately for the IO and PO periods.

Neurodevelopmental Testing

Children were administered the Bayley Scales of Infant and Toddler Development, Third Edition²⁰ by a clinical psychologist. The Bayley Scales of Infant and Toddler Development, Third Edition assesses developmental functioning through items administered in a structured play format. Compared with the second edition of the Bayley Scales, this updated measure

allows for the calculation of separate cognitive, receptive communication, and expressive communication scaled scores (previously combined into the Mental Development Index) and separate fine and gross motor scaled scores (previously combined into the Psychomotor Development Index). Scaled scores have a mean of 10 and a standard deviation of 3. We obtained only partial ND data for 5 patients because of child fussiness or time constraints. All available data for these patients were included in analyses.

Analytic Strategy

Exploratory univariable analyses assessed the relationships of NIRS measures and sociodemographic and clinical variables to ND scores. Receiver operating characteristic (ROC) analyses were then conducted to evaluate whether NIRS measures could be used to determine risk for ND delay, and if so, to identify the optimal threshold for ruling in and out delay. Only those relationships with a *P* value less than .10 in exploratory analyses were included in ROC analyses. Area under the curve (AUC) was reported as the measure of effect size, with 0.56 signifying the minimum for a small effect, 0.64 signifying the minimum for a medium effect, and 0.71 signifying the minimum for a large effect.²¹ For the purposes of ROC analyses, patients were stratified into 2 groups for each ND domain. Patients were considered delayed if their score was more than 1 standard deviation below the normative mean (scaled scores of 1-6). All other patients were considered nondelayed.

To evaluate whether NIRS measures make a significant contribution to the prediction of ND scores when considered in conjunction with other patient- and procedure-related variables, stepwise linear regression analyses were conducted. Dichotomous (greater than and less than identified thresholds) NIRS measures and sociodemographic and clinical characteristics significantly associated with ND scores in univariable analyses were considered for entry into multivariable models (see list in [Table E1](#)). Explained variance for all models was calculated by adjusted *R*² values. The Nemours Foundation was not involved in data interpretation.

RESULTS

Clinical Characteristics

[Table 1](#) shows the clinical and sociodemographic characteristics of the 31 participants in this sample. Cardiac procedures consisted of the Norwood (N = 6), ventricular septal defect repair (± coarctation) (N = 5), arch repair (N = 3), arterial switch (± ventricular septal defect repair) (N = 3), hemi-Fontan (N = 2), Ross-Konno (± arch repair) (N = 2), total anomalous pulmonary venous connection repair (N = 2), double-outlet right ventricle repair (N = 2), tetralogy of Fallot repair (N = 2), orthotopic heart transplantation (N = 1), truncus repair (N = 1), hybrid II (N = 1), and cor triatriatum repair (N = 1). One patient had cardiac arrest and required extracorporeal membrane oxygenation before the 24-month ND assessment. Procedure-related characteristics referred to the first (N = 29) or second (N = 2) procedure with CPB for which perioperative NIRS data were available. Five patients underwent 1 additional cardiac procedure, 10 patients underwent 2 additional cardiac procedures, and 1 patient underwent 3 additional cardiac procedures before the 24-month ND assessment. Among these patients, the first procedure was typically the most complex intervention, often performed during the newborn period. [Table 2](#) shows the perioperative NIRS data. Single ventricle physiology was associated with

TABLE 1. Clinical and sociodemographic characteristics

Clinical characteristics	Median (1Q-3Q)
Birth weight (kg)	3.2 (2.7-3.5)
Age at surgery (mo)	0.4 (0.1-2)
Weight at surgery (kg)	3.6 (3.2-4.3)
Aristotle complexity score	13 (10-15.5)
CPB support (min)	106.5 (75.8-131)
DHCA (min)	42.0 (35-50)
CICU stay (d)	9 (4-12)
Hospital stay (d)	17 (12-23)
Cumulative exposure to DHCA (min)	45 (35-80)
Clinical characteristics	Frequency (%)
Premature birth (<37 wk)	3 (10%)
Significant comorbidity*	8 (25.8%)
Single ventricle physiology	10 (32.3%)
Preoperative CICU	21 (67.7%)
Use of DHCA	29 (93.5%)
Preoperative cyanosis	16 (51.6%)
Multiple cardiac procedures (lifetime)	16 (51.6%)
Multiple procedures with DHCA (lifetime)	11 (35.4%)
Sociodemographic characteristics	Frequency (%)
Race/ethnicity	
Non-Hispanic white	24 (77.4%)
Black or African-American	5 (16.1%)
Other	2 (6.4%)
Household income	
<\$39,999	8 (25.8%)
\$40,000-\$69,999	6 (19.4%)
\$70,000-\$99,999	7 (22.6%)
>\$100,000	7 (22.6%)
Missing	3 (9.7%)
Education level of accompanying parent	
College degree or higher	15 (50%)
Education level of spouse/partner	
College degree or higher	16 (57.1%)

1Q, First quartile; 3Q, third quartile; CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest; CICU, cardiac intensive care unit. *Significant comorbidities included prematurity less than 35 weeks gestational age, arrhythmia, necrotizing enterocolitis, depressed myocardial function, protein losing enteropathy/right ventricle dysfunction/pacemaker, and pancreatic insufficiency.

lower preoperative rSO₂ ($t[29] = -2.0$, $P = .05$) and PO rSO₂ nadir ($t[29] = -4.9$, $P < .001$), and duration of DHCA was negatively associated with IO rSO₂ nadir ($r = -0.42$, $P = .02$) and PO rSO₂ nadir ($r = -0.41$, $P = .02$). PO rSO₂ nadir was significantly associated with PO lactate levels at 8 hours ($r = -0.40$, $P = .02$), but not at 16 ($r = -0.24$, $P = .19$) or 24 ($r = -0.14$, $P > .20$) hours, when the majority of lactate levels were less than 2 (84% and 79%, respectively).

Neurodevelopmental Outcomes

Mean scores for the cognitive (8.8 ± 3.3), receptive communication (9.3 ± 3.8), expressive communication (9.8 ± 4.0), and fine motor (10.2 ± 2.8) domains did not differ significantly from population means (10 ± 3), whereas

TABLE 2. Near-infrared spectroscopy data

	Preoperative	Intraoperative	Postoperative
rSO ₂ (%)	71 (53-80)	—	—
rSO ₂ nadir (%)	—	41 (33-46)	55 (41-61)
rSO ₂ % decrease	—	36.1 (26.6-50)	20.5 (1.4-36)
	Intraoperative	Postoperative	
rSO ₂ nadir			
<30%	4 (12.9%)	1 (3.2%)	
30%-39%	9 (29%)	5 (16.1%)	
40%-49%	12 (38.7%)	6 (19.4%)	
≥50%	6 (19.4%)	19 (61.3%)	
rSO ₂ % decrease			
≥50%	8 (25.8%)	2 (6.5%)	
40%-49%	6 (19.4%)	5 (16.1%)	
30%-39%	8 (25.8%)	3 (9.7%)	
20%-29%	6 (19.4%)	7 (22.6%)	
<20%	3 (9.7%)	14 (45.2%)	

rSO₂, Regional cerebral oxygen level. Reported as median (1Q-3Q) or frequency (percentage).

the mean score for the gross motor (8.3 ± 1.5) domain was lower than published norms ($P < .001$). Five patients (17%) were delayed (>1 standard deviation below the normative mean) in cognitive development, 7 patients (23%) were delayed in receptive communication, 5 patients (18%) were delayed in expressive communication, 2 patients (7%) were delayed in fine motor development, and 3 patients (11%) were delayed in gross motor development.

Table 3 shows the univariable correlations among preoperative, IO, PO, and perioperative NIRS measures and ND scores. The IO percent decrease was less than 20% in 3 patients who had diagnoses of hypoplastic left heart syndrome ($N = 2$) and transposition of the great arteries ($N = 1$) and whose baseline rSO₂ were within the first quartile for this sample. A closer look at the data revealed that the small IO percent decrease was likely a function of low baseline rSO₂, and that inclusion of patients with less than 20% decrease in the context of low baseline rSO₂ masked the negative relationship between IO percent decrease and language outcomes. After excluding these 3 patients, the correlation between IO percent decrease and receptive communication increased from $r = -0.08$ to $r = -0.44$ and the correlation between IO percent decrease and expressive communication increased from $r = -0.02$ to $r = -0.37$.

Receiver Operating Characteristic Analyses

ROC analyses evaluated whether preoperative rSO₂ could be used to determine the risk of cognitive delay, whether IO percent decrease could be used to determine the risk of receptive communication and expressive communication delays, and whether PO rSO₂ could be used to determine the risk of cognitive and gross motor delays, because these relationships had a significance level of P less than .10 in exploratory correlational analyses. Table E2

TABLE 3. Univariable correlations between near-infrared spectroscopy data and neurodevelopmental outcomes

	Cognitive	Receptive communication	Expressive communication	Fine motor	Gross motor
Preoperative rSO ₂	0.31	0.07	0.14	0.19	0.09
Perioperative rSO ₂ nadir*	0.28	0.26	0.23	0.04	0.12
IO rSO ₂ nadir	0.21	0.29	0.28	−0.01	0.03
PO rSO ₂ nadir	0.32	0.06	−0.03	0.18	0.37
Perioperative % decrease†,‡	−0.29	−0.39§	−0.28	−0.11	−0.13
IO % decrease‡	−0.23	−0.44§	−0.37	−0.09	−0.08
PO % decrease	0.03	0.02	0.09	−0.02	−0.22

rSO₂, Regional cerebral oxygen level; IO, intraoperative; PO, postoperative. *Refers to the lowest rSO₂ over the preoperative, IO, and PO periods. †Refers to the greatest percent decrease from baseline rSO₂ over the IO and PO periods. ‡Analyses exclude the 3 patients who had less than a 20% decrease from baseline rSO₂ during the IO period. §P < .05. ||P < .10.

displays sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) estimates for optimal and alternative thresholds.

Preoperative rSO₂ was not useful for prediction of cognitive delay (AUC, 0.53). IO percent decrease was moderately useful for prediction of receptive communication delay (AUC, 0.63), but not for prediction of expressive communication delay (AUC, 0.55). The optimal threshold for predicting receptive communication delay was 52% IO decrease from baseline, which had a sensitivity of 75%, specificity of 83%, PPV of 43%, and NPV of 95%. Patients with IO percent decrease greater than 52% (N = 7) had lower receptive communication scores than patients with IO percent decrease less than 52% (N = 21) (*t*[26] = 2.3, *P* = .03). Figure 1 shows the scores across all 5 ND domains for patients with an IO percent decrease greater than and less than 52%.

PO rSO₂ nadir was predictive of both cognitive delay (AUC, 0.66) and gross motor delay (AUC, 0.60). The optimal PO rSO₂ nadir threshold for predicting cognitive delay was 56%, which had a sensitivity of 100%, specificity of 56%, PPV of 31%, and NPV of 100%. Patients with a PO rSO₂ nadir less than 56% (N = 16) had lower

cognitive scores than patients with a PO rSO₂ nadir 56% or greater (N = 14) (*t*[28] = −2.8, *P* = .01). Figure 1 shows the scores across all 5 ND domains for patients with a PO rSO₂ nadir greater than and less than 56%. The optimal PO rSO₂ nadir threshold for predicting gross motor delay was 49%, which had a sensitivity of 67%, specificity of 67%, PPV of 20%, and NPV of 94%. Patients with a PO rSO₂ nadir less than 49% (N = 12) had lower gross motor scores than patients with a PO rSO₂ nadir 49% or greater (N = 19) (*t*[25] = −2.5, *P* = .02).

Multivariable Linear Regression Models

Table 4 shows the final multivariable models for each ND outcome.

Cognitive outcome. The final multivariable model for cognitive outcome consisted of length of hospital stay and PO rSO₂ nadir less than 56%, which together accounted for 37% of the variance. Of note, the observed relationship between PO rSO₂ nadir less than 56% and cognitive outcome appears independent of baseline rSO₂, preoperative cyanosis, and IO rSO₂ nadir, because the strength of this relationship (*r* = −0.46) did not meaningfully change when controlling for baseline rSO₂ (*r* = −0.46), preoperative cyanosis (*r* = −0.44), or IO rSO₂ nadir (*r* = −0.43), or after

FIGURE 1. ND outcomes of patients with an IO percent decrease from baseline rSO₂ greater than and less than 52% and a PO rSO₂ nadir greater than and less than 56%. Scores have a normative mean of 10 and standard deviation of 3. IO % Dec, Intraoperative percent decrease from baseline rSO₂; PO rSO₂, lowest postoperative regional cerebral oxygen saturation (nadir); Cog, cognitive; RC, receptive communication; EC, expressive communication; FM, fine motor; GM, gross motor.

TABLE 4. Final stepwise linear regression models

	B	SE (B)	β	P	R ²
Regression 1: cognitive					.37
Length of hospital stay	−0.04	0.02	−.44	.009	
PO rSO ₂ nadir < 56%	−2.5	1.0	−.39	.02	
Regression 2: RC*					.13
IO % decrease > 52%	−3.4	1.5	−.40	.03	
Regression 3: fine motor					.23
Length of CICU stay	−0.05	0.02	−.51	.007	
Regression 4: gross motor					.46
Multiple DHCA	−1.8	0.45	−.59	.001	
Parent education level	1.3	0.43	.44	.006	

SE, Standard error; PO, postoperative; rSO₂, regional cerebral oxygen level; RC, receptive communication; IO, intraoperative; CICU, cardiac intensive care unit; DHCA, deep hypothermic circulatory arrest. *Analyses exclude the 3 patients who had less than a 20% decrease from baseline rSO₂ during the intraoperative period.

excluding patients with baseline rSO₂ less than 40% ($r = -0.43$). Neither single ventricle physiology nor duration of DHCA entered into the final stepwise regression model. When duration of DHCA was forced into the model, the added predictive value of PO rSO₂ nadir less than 56% remained marginally significant ($\Delta R^2 = 0.11$, $P = .052$). When single ventricle physiology was forced into the model, the added predictive value of PO rSO₂ nadir less than 56% did not reach statistical significance ($\Delta R^2 = 0.08$, $P = .11$).

Language outcomes. The final multivariable model for receptive communication outcome consisted of IO percent decrease greater than 52%, which accounted for 13% of the variance. No clinical or sociodemographic characteristics were associated with expressive communication outcome.

Motor outcomes. The final multivariable model for fine motor outcome included length of cardiac intensive care unit stay, which accounted for 23% of the variance. The final multivariable model for gross motor outcome consisted of education level of accompanying parent and multiple procedures with DHCA, which together accounted for 46% of the variance.

DISCUSSION

Because of dramatic improvements in survival after surgical repair of CHD, identification of strategies to improve ND outcome has become the next challenge. NIRS monitoring has emerged as a surrogate means of evaluating rSO₂ and has been introduced into clinical practice in the absence of empirical and reproducible data relating NIRS values to ND outcome. The limited research to date has focused exclusively on rSO₂ during the preoperative or intraoperative periods, despite studies documenting decreased oxygen delivery during the early PO period¹²⁻¹⁵ and an association between PO events and neurologic or ND outcomes.¹⁶⁻¹⁸

In this cohort, the relative IO decrease from baseline rSO₂ was associated with receptive communication outcome, whereas the rSO₂ nadir during the PO period was associated with cognitive outcome. This suggests that perioperative NIRS monitoring may enhance our ability to predict ND outcomes beyond what is possible when considering other clinical characteristics or monitoring methods. These results also suggest that the specific NIRS measures associated with ND outcome differ across the continuum of the perioperative period. Percent decrease from baseline rSO₂ had greater predictive value for ND outcome during the IO period; this may reflect the fact that the baseline was established at the beginning of the procedure after induction of anesthesia, and the lowest values were commonly reached in association with important changes in perfusion, allowing for a broader range of change during the IO period. Our results also suggest that the specific ND domain associated with decreased rSO₂ may differ across

the perioperative period. Although this may be a function of limited statistical power given the small sample size, this could also indicate that different areas of the brain exhibit different thresholds to hypoxic injury.

Results from the IO period are generally consistent with our prior work, which revealed a relationship between rSO₂ and receptive communication, but not other ND domains.¹¹ It is interesting that IO rSO₂ seems to have a more robust relationship with receptive, compared with expressive, communication. It is possible that performance on this domain reflects not only language development but also attentional abilities, known to be affected among children with complex CHD.²² Poor focus or impulsivity could negatively affect a child's performance on receptive communication tasks, which require the child to attend to the examiner's verbal cues, to determine which pictures or objects correspond with each verbal cue, and to follow directions. Kussman and colleagues⁹ found an association between IO rSO₂ and the Psychomotor Development Index, but not the Mental Development Index, of the second edition of the Bayley Scales in a cohort of patients undergoing biventricular repair. However, the study by Kussman and colleagues differed from the current investigation with regard to the cardiac diagnoses of the sample, need for additional cardiac surgeries before testing, ND testing battery, and age at which children were tested, making cross-study comparisons difficult.

The current study extends prior work on the assessment of rSO₂ by including rSO₂ values during the early PO period, therefore evaluating the clinical utility of PO NIRS monitoring to predict ND outcomes while considering important clinical variables. The NIRS threshold with the best balance of sensitivity and specificity was an IO percent decrease from baseline rSO₂ of 52%, which correctly classified 75% of children with receptive communication delay and 87% of children without delay. A patient whose IO rSO₂ remains within 52% of the baseline value has a 95% chance of experiencing normal receptive communication development on the basis of this patient cohort. A PO rSO₂ nadir threshold of 56% correctly classified 100% of children with cognitive delay, and a patient whose PO rSO₂ nadir is at or greater than 56% has a 100% chance of experiencing normal cognitive development on the basis of this cohort. However, the specificity of this measure for cognitive delay was not sufficiently better than chance. On the basis of these results, perioperative NIRS data could be used in clinical practice to predict which children are at highest risk for delay and in need of early intervention and which are likely to exhibit typical development. However, these data must be validated in a prospective cohort. In addition, prospective studies are necessary to evaluate whether NIRS can be used to guide perioperative management decisions and, more important, to improve ND outcome. Without these data, the clinical utility of perioperative NIRS is likely to remain a topic of controversy.

In the past, optimal NIRS measurements have not been defined. Thresholds for high risk have been assigned in the absence of empirical studies directly examining their relationship to ND outcome.⁶ We used an empirical method to determine optimal thresholds, and the differences between these thresholds and those previously suggested to be associated with increased risk are notable. The identified IO percent decrease from baseline rSO₂ threshold of 52% is larger than the previously suggested decrease of 20%.⁶ Because nearly all patients experienced at least a 20% decrease from baseline in the IO period, a 20% threshold lacks specificity. It should also be noted that in this cohort, the 3 patients who exhibited less than a 20% decrease from baseline during the IO period had low baseline rSO₂ and exhibited significant ND impairments. Therefore, caution should be exercised when considering percent decrease as an isolated measure. The PO rSO₂ nadir threshold of 56% is more conservative than the previously recommended value of 40%.⁶ Perhaps this is a reflection of the different conditions patients encounter during the PO period, including normothermia and increased activity, which are likely to affect the metabolic rate of oxygen in the brain.

Because of the variability regarding the most predictive rSO₂ measure and the most affected ND domain between the IO and PO periods, it was not possible to determine if and how the optimal threshold for a single rSO₂ measure would change over the perioperative period. However, the pattern of results suggests that optimal thresholds for IO rSO₂ may be higher than for PO rSO₂. This may be related to the neuroprotection conferred by the use of hypothermia during the IO period. It should also be noted that rSO₂ nadir and percent decrease from baseline rSO₂ showed weaker relationships to ND outcome when the entire continuum of the perioperative period was considered, compared with when the IO and PO periods were considered independent of one another. These data suggest that emphasis on one single NIRS measure or threshold across the continuum of the perioperative period may not be clinically useful.

Of note and consistent with prior research,^{11,23} the length of cardiac intensive care unit and total hospital stay remained a robust predictor of neurodevelopment, even when other patient- and procedure-related variables were considered. Infants who experience a prolonged hospital stay are likely sicker, are prone to complications, and may be missing important experiences and opportunities that would promote their early development. The observed relationship between parent education level and neurodevelopment is consistent with previously documented relationships between socioeconomic status measures and neurodevelopment.²⁴ This is likely driven by multiple factors, including access to financial and educational resources and underlying genetic differences that contribute to both parent academic achievement and early childhood development.

Study Limitations

Limitations of this study include its small sample size and cross-sectional retrospective design, which precludes conclusions regarding causality. This article reports on secondary analyses of patients enrolled across 2 research studies examining ND outcomes after infant cardiac surgery. Patients included in these analyses underwent more complex procedures with longer support times and greater use of DHCA when compared with the broader population of infants undergoing cardiac surgery. These findings may not generalize to patients who do not have DHCA. It should also be noted that half of the participants in this study had multiple surgeries and hospitalizations; therefore, although the primary focus of this study was on the first surgery with CPB during which patients received perioperative NIRS monitoring, it is possible that events occurring during other perioperative periods affected ND outcomes. Last, because PO NIRS values were entered into the medical record on an hourly basis, cumulative minutes at or below a particular rSO₂ could not be calculated and brief decreases in rSO₂ may not be captured in the available data.

CONCLUSIONS

NIRS monitoring during and beyond the IO period seems to enhance the ability to predict ND outcomes at 2 years of age. Specific NIRS measures associated with ND outcome and the optimal thresholds on these measures differ across the continuum of the perioperative period. The use of a single NIRS measure or threshold across the continuum of the perioperative period may not be appropriate. Further research is needed to investigate these relationships in a prospective manner and to examine whether goal-directed therapy can alter NIRS measurements and long-term ND outcomes.

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Discussion

Dr Charles Fraser (Houston, Tex). I congratulate Dr Sood and colleagues from Nemours Cardiac Center for this body of work adding further information to this ongoing and sometimes curious debate about the benefits of NIRS in providing relevant perioperative physiologic monitoring and potentially optimizing ND outcomes in children with critical cardiac disease undergoing surgery.

Without attempting to resummmary this well-written manuscript and elegant presentation that we've just heard, I synopsise

this work as follows: In a heterogeneous group of 31 children undergoing repair in infancy, 8 of whom had single ventricles, using various CPB strategies but a lot of circulatory arrest, you've observed and concluded that perioperative NIRS monitoring has predictive utility in ultimate ND outcome. Specific observations included noting that a 52% decrease from baseline IO NIRS saturation correctly classified 75% of children with receptive communication delay and that a PO threshold of 56% correctly classified 100% of children with cognitive delay.

As the authors probably know, these data are somewhat consistent with ours from Texas Children's Hospital as recently presented at the Society of Thoracic Surgeons meeting in Florida by my colleague Dean Andropoulos. We presented there and will soon report in print our findings that low perioperative cerebral cortical oxygen saturations as measured by NIRS has a direct relationship with 12-month Bayley developmental scores. To our view, and apparently now yours, measuring oxygen delivery to the brain has clinical relevance in predicting outcome.

You note that 94% of the children had circulatory arrest. Other than the isolated measured data points documenting the lowest IO saturations, were you able to measure the total time spent at nadir? We should probably ask the same questions about preoperative and PO levels.

Dr Sood. We did not measure total time spent at nadir. This study examined NIRS data collected using the prior software, which did not report AUC. Also, we obtained PO NIRS data from the medical record, which were entered on an hourly basis. However, we examined total time spent below specific NIRS thresholds in our prior study of IO NIRS and did not find an association with ND outcomes. Kussman and colleagues⁹ examined the relationship between IO NIRS data and ND outcomes at 1 year of age and did not find an association between AUC for rSO₂ less than or equal to 45% and ND outcomes. But certainly this needs to be further examined in future studies.

Dr Fraser. Well, that's a good segue into question 2. Your group has published 3 related abstracts on this subject in the last 4 months. In the January issue of the *Journal* you concluded, and I quote: "In a contemporary cohort of infants undergoing surgery for congenital heart disease, neurodevelopmental outcomes at 2 years are largely influenced by patient-related characteristics. Although receptive communication appears to be influenced by the NIRS nadir, the predictive value remains unclear."

Elsewhere in this meeting's program, there is a poster abstract in which you conclude, apparently in the same group of patients, that "duration of hypothermic circulatory arrest was not predictive of any neurodevelopmental outcome."

Finally, in this article you conclude, "NIRS monitoring during and beyond the IO period seems to enhance the ability to predict ND outcomes at 2 years of age." So please help me tie this all together.

Dr Sood. Our recent article in the *Journal* reported on only IO data, and the results were generally consistent with what was found in the present study. The prior study found a relationship between IO NIRS nadir and receptive communication outcome, and the present study found a relationship between IO percent decrease from baseline and receptive communication outcome. The relationship that we previously described between IO NIRS nadir and receptive communication did not reach statistical significance

in the present sample. However, receptive communication was the domain associated with NIRS data in both studies.

Although the study samples for the 3 abstracts that you referred to do overlap, they are not equivalent samples. Additional patients have been tested since the 2 prior abstracts, and the specific inclusion criteria differ across studies. For example, several patients included in the IO NIRS study were excluded from this study because perioperative NIRS data were not available.

Dr Christian Pizarro (*Wilmington, Del*). Maybe I could help with that answer. I think that last year when we presented some of these data at the meeting in Philadelphia, the question was raised to the fact that there were no PO data, and obviously things could occur in that immediate period, particularly in the first 48 hours, and that was the stimulus for us to go back and try to obtain and look at the PO data and NIRS monitoring.

Now, the challenge was that not every patient had PO NIRS data available, and therefore that's why there is a slight difference in which patients were included in each study. But the idea for this particular project was to look at all patients who had NIRS data available before, during, and after surgery.

Dr Fraser. Christian might want to comment on this as well. In the last sentence of your conclusion in the article you state that "Further research is needed to investigate these relationships in a prospective manner and to examine whether goal-directed therapy can alter NIRS measurements and long-term ND outcomes."

As we talked about earlier, first, you can alter NIRS measurements with direct interventions (eg, higher hematocrit, higher flow rates). On the basis of what you've learned so far, do you plan to change your strategy going forward and act on the NIRS information rather than just observe it?

Dr Pizarro. That's a great question. Part of the challenge is the fact that when it comes to IO interventions, obviously the intuitive mode of treatment would be to alter perfusion, for example, use regional antegrade cerebral perfusion; however, we do not know the true impact of this strategy that may increase cerebral edema, for example. This is different than increasing the hematocrit in the

intensive care unit or giving inotropes and trying to augment cardiac output by other means. So as stated before, CPB is probably an unnatural state, and there is some potential morbidity from it.

If we look at the Michigan study where randomization of regional cerebral perfusion and circulatory arrest was undertaken, actually no difference was demonstrated. Although we could alter the number that the NIRS monitor gives us, the consequences and the impact of the measures that we used to achieve that might not necessarily improve the overall outcome. What we discovered through this analysis is that it seems like the cutoff, of 40% as a nadir, might be too low, and data would suggest that perhaps the cutoff is in the 50s. We would be inclined to continue to explore this, enroll more patients to include in the analysis, and probably, if the data sustain the study's findings, modify our approach to it.

Dr J. William Gaynor (*Philadelphia, Pa*). I agree with your final statement. We have to be careful about using historical controls. This is an important first step, along with the data from Texas Children's, that we're beginning to get data that may correlate some of these measurements at certain time points, and particularly in the PO period, with ND outcomes. These type of data will be important, although it take some time before it becomes completely ingrained in clinical practice.

We recently did a systematic review of the literature for many of the things that we do for neuroprotection and neuromonitoring, and the level of evidence for what we do is appalling. There is almost nothing that reaches class 1 evidence. We have an opportunity if people will be willing to design appropriate trials, based on this type of evidence, to begin to look at NIRS in a formal prospective way with evaluation of goal-directed therapy.

Some of the work by Dr Licht has suggested that increasing delivery may not be the best thing. Perhaps we have to decrease demand, for example, keeping patients intubated or sedated longer, perhaps cooling a little bit. I don't know. If we begin to have some idea of the balance between oxygen use and oxygen delivery, then we should design a trial, so going forward we actually have evidence for some of the things we do.

TABLE E1. Clinical and sociodemographic characteristics and near-infrared spectroscopy measures considered for entry into stepwise linear regression models

		Univariable correlations with ND outcome				
		<i>r</i>	<i>P</i>		<i>r</i>	<i>P</i>
Cognitive					Fine motor	
Single ventricle physiology*	−0.40	.03		Parent education level	0.40	.04
Significant comorbidity*	−0.41	.02		Length of CICU stay	−0.51	.007
Duration of DHCA	−0.39	.03		Length of hospital stay	−0.47	.01
PO rSO ₂ nadir < 56%	−0.46	.01		Gross motor		
Length of CICU stay	−0.46	.01		Parent education level	0.39	.047
Length of hospital stay	−0.52	.003		Significant comorbidity	−0.43	.03
Multiple DHCA*	−0.41	.02		Preoperative cyanosis*	−0.45	.02
Receptive communication				Duration of DHCA	−0.44	.02
IO rSO ₂ % decrease > 52%†	−0.40	.03		PO rSO ₂ nadir < 49%	−0.46	.01
Expressive communication				Length of CICU stay	−0.46	.02
None				Length of hospital stay	−0.45	.02
				Multiple DHCA	−0.55	.003
				Cumulative DHCA	−0.44	.02

ND, Neurodevelopmental; DHCA, deep hypothermic circulatory arrest; PO, postoperative; rSO₂, regional cerebral oxygen level; CICU, cardiac intensive care unit; IO, intraoperative. *Dichotomous variables were coded as present (1) or absent (0). †Analyses exclude the 3 patients who had less than a 20% decrease from baseline to intraoperative rSO₂ nadir.

TABLE E2. Clinical utility estimates for intraoperative and postoperative near-infrared spectroscopy thresholds

ND domain/NIRS measure	AUC	Threshold	Sensitivity	Specificity	PPV	NPV
Receptive communication						
IO % decrease*	0.63	49.7	0.75	0.79	0.38	0.95
		52.2	0.75	0.83	0.43	0.95
		54.6	0.50	0.83	0.33	0.91
Cognitive						
PO rSO ₂ nadir	0.66	57	1.00	0.48	0.28	1.00
		55.5	1.00	0.56	0.31	1.00
		53	0.80	0.60	0.29	0.94
Gross motor						
PO rSO ₂ nadir	0.60	52.5	0.67	0.58	0.17	0.93
		48.5	0.67	0.67	0.20	0.94
		43.5	0.33	0.67	0.11	0.89

Bold text signifies optimal thresholds based on the balance of sensitivity, specificity, positive predictive value, and negative predictive value. ND, Neurodevelopmental; NIRS, near-infrared spectroscopy; AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value; IO, intraoperative; PO, postoperative; rSO₂, regional cerebral oxygen level. *Analyses exclude the 3 patients who had less than a 20% decrease from baseline to intraoperative rSO₂ nadir.