Congenital Heart Disease

Relationship of Intraoperative Cerebral Oxygen Saturation to Neurodevelopmental Outcome and Brain Magnetic Resonance Imaging at 1 Year of Age in Infants Undergoing Biventricular Repair

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Background—Near-infrared spectroscopy monitoring of cerebral oxygen saturation (rSO2) has become routine in many centers, but no studies have reported the relationship of intraoperative near-infrared spectroscopy to long-term neurodevelopmental outcomes after cardiac surgery.

Methods and Results—Of 104 infants undergoing biventricular repair without aortic arch reconstruction, 89 (86%) returned for neurodevelopmental testing at 1 year of age. The primary near-infrared spectroscopy variable was the integrated rSO2 (area under the curve) for rSO2 ≥45%; secondary variables were the average and minimum rSO2 by perfusion phase and at specific time points. Psychomotor and mental development indexes of the Bayley scales, head circumference, neurological examination, and abnormalities on brain magnetic resonance imaging did not differ between subjects according to a threshold level for rSO2 of 45%. Lower Psychomotor Development Index scores were modestly associated with lower average (r=0.23, P=0.03) and minimum (r=0.22, P=0.04) rSO2 during the 60-minute period after cardiopulmonary bypass but not with other perfusion phases. Hemosiderin foci on brain magnetic resonance imaging were associated with lower average rSO2 from postinduction to 60 minutes post cardiopulmonary bypass (71±10% versus 78±6%, P=0.01) and with lower average rSO2 during the rewarming phase (72±12% versus 83±9%, P=.003) and during the 60-minute period following cardiopulmonary bypass (65±11% versus 75±10%, P=0.009). In regression analyses that adjusted for age ≤30 days, Psychomotor Development Index score (P=0.02) and brain hemosiderin (P=0.04) remained significantly associated with rSO2 during the 60-minute period following cardiopulmonary bypass.

Conclusions—Perioperative periods of diminished cerebral oxygen delivery, as indicated by rSO2, are associated with 1-year Psychomotor Development Index and brain magnetic resonance imaging abnormalities among infants undergoing reparative heart surgery.

Clinical Trial Registration—URL: http://clinicaltrials.gov. Unique identifier: NCT00006183.

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Key Words: heart defects, congenital ★ brain ★ oxygen ★ spectroscopy, near-infrared ★ magnetic resonance imaging

As operative mortality rates for virtually all forms of congenital heart disease have declined, the focus has shifted to improving late functional outcome. Survivors of congenital heart disease have a significant prevalence of neurodevelopmental and behavioral disabilities. These have been linked, in part, to bypass-related variables and include lower scores on the Bayley Scales of Infant Development and longer-term impairments in cognitive abilities, gross and fine motor function, visual-spatial skills, speech and language, executive function, and attention. Identification of methods to reduce the frequency and severity of these adverse outcomes is therefore a high priority. Although neurodevelopmental outcomes of children with congenital heart disease are influenced by many factors, both innate and acquired, with...
cumulative effects, cerebral ischemia in the perioperative period is still an important cause of brain injury. Therefore, reliable methods for detecting cerebral ischemia may allow for management strategies to improve neurodevelopmental outcomes.

Clinical Perspective on p 254

The ability of near-infrared spectroscopy (NIRS) to measure cerebral oxygenation was first demonstrated by Jobsis. Animal studies have demonstrated a relationship of NIRS during cardiopulmonary bypass (CPB) to early neurological outcome. In humans, Austin et al reported that intraoperative interventions based on multimodality neurophysiological monitoring, including NIRS, during pediatric cardiac surgery reduced the incidence of postoperative neurological sequelae; however, the relationship of NIRS findings to long-term neurological outcome was not evaluated. Subsequent reports have shown that lower intraoperative cerebral oxygen saturation and prolonged low postoperative cerebral oxygen saturation are risk factors for white matter injury on brain magnetic resonance imaging (MRI). To monitor cerebral oxygen saturation, some investigators have advocated widespread adoption of NIRS during cardiac surgery. Indeed, NIRS monitoring has become routine in many centers. However, no studies have reported the relationship of intraoperative NIRS findings to long-term neurological outcome after cardiac surgery.

Our group has shown that intraoperative cerebral oxygen saturation in infants undergoing biventricular repair varies according to diagnosis and accounts for very little of the variance in early postoperative outcome. Specifically, no significant associations were found between cerebral oxygen saturation and lactate at 60 minutes after CPB, cardiac index at 6 and 18 hours after CPB, Pediatric Risk of Mortality (PRISM) III scores, and length of intubation, intensive care, and hospital stay. Additionally, area-under-the-curve analysis found no difference in early outcome between those subjects in whom the regional cerebral oxygen saturation (rSO2) remained above 45% versus those in whom it decreased to ≤45%. The aim of the present study was to evaluate the relationship of intraoperative cerebral oxygen saturation to neurological outcome at age 1 year, assessed by neurodevelopmental evaluation and brain MRI. We hypothesized that lower levels of intraoperative cerebral oxygen saturation would be associated with worse neurodevelopmental outcome.

Methods

Patients and Study Design

With Institutional Review Board approval and parental informed consent, patients were enrolled between April 2001 and July 2004 at Children’s Hospital Boston in a randomized trial of hemodilution to a hematocrit of 25% versus 35% during hypothermic CPB. Eligibility criteria included reparative heart surgery at <9 months of age in 3 diagnostic groups: (1) D-transposition of the great arteries; (2) tetralogy of Fallot, with or without pulmonary atresia or truncus arteriosus; and (3) ventricular septal defect or complete common atroventricular canal defect. Exclusion criteria included birth weight <2.3 kg, recognizable phenotypic syndrome of congenital anomalies, extracardiac anomalies of greater than minor severity, previous cardiac surgery, or associated cardiovascular anomalies requiring aortic arch reconstruction or additional open surgical procedures before the planned developmental follow-up.

Anesthesia and Perfusion Methods

Methods for anesthesia and perfusion have been described previously. Briefly, high-dose opioid-relaxant anesthesia (fentanyl 100 μg/kg) was supplemented with midazolam and/or isoflurane as tolerated. Bypass prime comprised whole blood and Plasma-Lyte A pH 7.4 (Multiple Electrolytes Injection, Type 1, USP) to attain a hematocrit of 25% or 35% at the time of onset of low-flow CPB. A pH-stat strategy was used during core cooling, low-flow hypothermic perfusion, and rewarming up to 30°C. Full-flow CPB was approximately 2.5 L · min⁻¹ · m⁻²; some patients had periods of deep hypothermic circulatory arrest, and most had at least 1 period of low-flow CPB of approximately 0.75 L · min⁻¹ · m⁻² when at deep hypothermia (rectal temperature <18°C). Methylprednisolone (30 mg/kg), phenolamine (0.2 mg/kg), and furosemide (0.25 mg/kg) were given at the initiation of CPB, and mannitol (0.5 g/kg) and phenolamine (0.2 mg/kg) were administered at the onset of rewarming. Patients were rewarmed for at least 30 minutes and to a rectal temperature of 34°C.

Near-Infrared Spectroscopy

Regional cerebral oxygen saturation (rSO2) was measured with the INVOS 5100B (Somanetics, Troy, Mich) as described previously. The INVOS is a continuous-wave near-infrared spectrometer that uses 2 wavelengths of light (730 and 810 nm) to measure the ratio of oxyhemoglobin to total hemoglobin to derive oxygen saturation, the scale unit of which is percent (%). Pediatric SomaSensors (Somanetics) were placed on the right and left forehead after induction of anesthesia and data collected continuously up to 60 minutes after CPB. Because cerebral oximetry was not a routine part of our practice at the time of the present study, perioperative management decisions were not made on the basis of cerebral oxygen saturation. The primary variable selected for evaluation of the relationship between rSO2 and neurodevelopmental outcome at age 1 year was the integrated rSO2 or area under the curve for rSO2 >45% (minutes × desaturation points ≤45%). Subjects who had at least 1 episode in which the rSO2 fell to ≤45% for a period of 1 minute (threshold level) were identified as having a decline in cerebral oxygen saturation to the defined cutoff value. Comparisons were then performed between 3 groups of subjects: Those in whom the rSO2 remained >45% (group I, area under the curve =0 min%), and those in whom the rSO2 fell to ≤45%, dichotomized by the median integrated rSO2 ≤45%, which was 40 min%. Group II subjects had an area under the curve >0 but <40 min%, and group III subjects had an area under the curve ≥40 min%. Integrated rSO2 was chosen over total duration of rSO2 ≤45% to better indicate the extent of desaturation below the threshold value. Laboratory and clinical studies suggest that NIRS thresholds for cerebral injury are oxygen saturations in the range of 33% to 55%. Cerebral oxygen saturations at these levels are associated with functional impairment (increased brain lactate, electroencephalogram changes, and decreased brain tissue ATP concentration), abnormal neurobehavioral examinations and brain histology, and new or worsened ischemia on postoperative brain MRI. Because a nonlinear relationship between rSO2 and neurodevelopmental outcome may exist, similar analyses were performed with 50% and 55% used as possible threshold values.

Secondary NIRS variables included the average rSO2 and minimum rSO2 for the time period from postinduction to 60 minutes post-CPB, as well as by perfusion phase: Postinduction to on-CPB, onset of cooling to onset of last rewarming, onset of last rewarming to off-CPB, and off-CPB to 60 minutes post-CPB. The rSO2 measurements at specified time points were also used as secondary variables.

Neurodevelopmental Outcomes

Neurodevelopmental evaluation at 1-year follow-up comprised neurological examination (also performed preoperatively), development-
nal evaluation, and brain MRI. Neurological examination was defined as abnormal if abnormalities were noted in any of the following categories: Head circumference, mental status, special senses, cranial nerve function, or peripheral motor function. Development was assessed with the Bayley Scales of Infant Development-II, which yield scores on 2 indexes, the Psychomotor Development Index (PDI) and the Mental Development Index (MDI).20 PDI scores were the primary outcome for the hematocrit trial16 from which these secondary analyses are derived. Brain MRIs were obtained in a subset of participants. MRI sequences have been described in detail elsewhere.21 Briefly, these sequences were a sagittal localizer and an axial multiplanar gradient recalled acquisition sequence for detection of old products of hemorrhage, 3-dimensional spoiled gradient recalled and dual fast spin echo sequences in the coronal plane for volumetric analysis, an axial diffusion tensor imaging sequence, and a single-voxel proton magnetic resonance spectroscopy sequence. The percent of white matter relative to whole brain volume was calculated by dividing the sum of the myelinated and unmyelinated white matter volume by the volume of the entire brain (ie, without cerebrospinal fluid included). All sequences were evaluated for evidence of acquired or developmental abnormalities by a single pediatric neuroradiologist (R.R.). A detailed description of the MRI data-acquisition parameters and data-processing techniques used to analyze the volumetric, diffusion tensor imaging, and magnetic resonance spectroscopy data has been reported previously.16,21

### Statistical Analysis

Comparisons of perioperative characteristics, NIRS values, and neurodevelopmental outcomes across categories of integrated rSO2 ≤45% were made with ANOVA for continuous variables and the Fisher exact test for categorical variables. Analyses of PDI and MDI scores also adjusted for social class,22 and analyses of quantitative MRI variables also adjusted for age at MRI evaluation. Partial Spearman rank correlation coefficients, adjusted for age at MRI evaluation, were used to assess associations between NIRS measures and quantitative MRI measures. We used t tests and logistic regression to assess associations between NIRS measures and binary MRI abnormalities. We also considered linear and logistic regression models that adjusted for neonatal status or diagnosis group. In this secondary analysis of data arising from a clinical trial, a sample size of 89 subjects provided 80% power to detect correlations of 0.30 or larger in a 2-sided 0.05 level test of the null hypothesis of no correlation.

### Results

Of 104 infants who had NIRS monitoring in the primary study, 89 (86%) returned for testing at age 1 year. Of the remaining 15 families, 12 refused to participate, 2 lived outside the country and were not invited for 1-year follow-up, and 1 agreed to questionnaires only. Subjects who returned for 1-year follow-up were similar to those who declined with respect to perioperative characteristics and NIRS measurements.

Demographic and perioperative characteristics according to the primary variable, integrated rSO2 ≤45%, are shown in Table 1. NIRS data according to categories of integrated rSO2 ≤45% are shown in Table 2. The integrated rSO2 ≤45% was 0 min% for group I, ranged from 0.3 to 39 min% for group II, and ranged from 60 to 383 min% for group III. No infant had clinical seizures or stroke perioperatively. Group III had the longest total support time, cross-clamp time, and duration of circulatory arrest, with trends toward longer low-flow bypass and diagnosis of D-transposition of the great arteries. The NIRS groups did not differ in hematocrit at any time point, nadir temperature ( tympanic 20 ±5°C), lowest pO2 (99±80 mm Hg), lowest Pco2 (33±4 mm Hg), or highest Pco2 (761±4 mm Hg).

### Table 1. Preoperative and Operative Characteristics According to Categories of Integrated rSO2 ≤45%

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preoperative characteristics</th>
<th>Operative characteristics</th>
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<tbody>
<tr>
<td></td>
<td>0 min% (n=66)</td>
<td>0.3–39 min% (n=12)</td>
</tr>
<tr>
<td>Preoperative characteristics</td>
<td></td>
<td></td>
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<tr>
<td>Birth weight, kg</td>
<td>3.5±0.5</td>
<td>3.3±0.6</td>
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<tr>
<td>Gestational age, wk</td>
<td>39.2±1.3</td>
<td>39.2±1.6</td>
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<tr>
<td>Sex, % male</td>
<td>64</td>
<td>42</td>
</tr>
<tr>
<td>Race, % nonwhite</td>
<td>20</td>
<td>33</td>
</tr>
<tr>
<td>Age at surgery, d, median (range)</td>
<td>38 (2–200)</td>
<td>64 (4–263)</td>
</tr>
<tr>
<td>Neonatal status, % age ≥30 d</td>
<td>48</td>
<td>33</td>
</tr>
<tr>
<td>Abnormal neurological examination, n/total (%)</td>
<td>27/47 (57)</td>
<td>6/9 (67)</td>
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<tr>
<td>Diagnosis, n (%)</td>
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<td></td>
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<tr>
<td>TGA</td>
<td>28 (42)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>TOF</td>
<td>26 (39)</td>
<td>5 (42)</td>
</tr>
<tr>
<td>VSD</td>
<td>12 (18)</td>
<td>5 (42)</td>
</tr>
<tr>
<td>Operative characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross-clamp time, min</td>
<td>65±23</td>
<td>60±29</td>
</tr>
<tr>
<td>Total support time, min</td>
<td>104±30</td>
<td>101±38</td>
</tr>
<tr>
<td>Total bypass time, min</td>
<td>95±24</td>
<td>95±36</td>
</tr>
<tr>
<td>Low-flow bypass time, min</td>
<td>48±23</td>
<td>47±31</td>
</tr>
<tr>
<td>Duration of circulatory arrest, min</td>
<td>8±11</td>
<td>5±13</td>
</tr>
</tbody>
</table>

TGA indicates D-transposition of the great arteries; TOF, tetralogy of Fallot; and VSD, ventricular septal defect. Values are expressed as mean±SD. P values are determined by ANOVA for continuous variables and Fisher exact test for categorical variables.
PDI and MDI scores for the entire cohort were 87±16 and 94±12, significantly lower than population norms with a mean of 100 (P<0.001 for each). PDI scores did not vary significantly among the 3 NIRS groups classified by integrated rSO2 ≤45% (Table 3). Furthermore, the partial Spearman correlation with adjustment for social class found no relationship between integrated rSO2 ≤45% measured on a continuous scale and PDI score. When examined by perfusion phase, PDI was significantly correlated with average rSO2 (r=0.23; P=0.04) and minimum rSO2 (r=0.22; P=0.04) during the 60-minute period after cessation of CPB (off-CPB to 60 minutes post-CPB; Figure 1) but not with any other perfusion phase. Evaluation of PDI with rSO2 at each time point found significant correlations at 10 minutes of cooling (r=0.24, P=0.03), at off-CPB (r=0.25, P=0.02), and at 60 minutes post-CPB (r=0.22, P=0.04) but no correlations at 6 and 18 hours post-CPB. PDI did not correlate with the difference in rSO2 between onset of cooling (64±14%) and at 10 minutes of cooling (86±9%). No correlation was found between any intraoperative NIRS variable and MDI score.

Mean head circumference (z score) for the cohort at 1-year follow-up was −0.03±1.01 and did not differ between the 3 integrated rSO2 ≤45% groups (Table 3). No correlation was found between any intraoperative NIRS variable and head circumference at age 1 year. Neurological examination was abnormal in 50 subjects (60%) at age 1 year, but no difference in intraoperative NIRS variables was found between those subjects with a normal versus an abnormal neurological examination.

Brain MRI scans were obtained in 40 of the 89 subjects who had measurement of intraoperative cerebral oxygen saturation. Missing MRI scans were due to parental refusal, usually related to the need for general anesthesia (n=47), and cancellations by the anesthesiologist that related to medical concerns (n=2). Subjects who had an MRI scan were similar with respect to scores on the Bayley Scales of Infant Development-II and on neurological examination to those subjects whose parents declined the MRI scan.21 There was no evidence of severe brain injury or major brain malformations. The majority of acquired abnormalities were tiny foci of signal abnormality on the multiplanar gradient recalled sequence consistent with small foci of hemosiderin (Table 3). These foci were found in 14 of this subset of 40 subjects (35%) and were present throughout the entire brain, without predilection for any particular region or specific pattern of distribution. Analysis of the relationship according to integrated rSO2 ≤45% categories and qualitative MRI measures found no significant association with the presence of foci of hemosiderin or other developmental or acquired abnormalities. Similarly, we found no statistically significant relationship between integrated rSO2 ≤45% measured on a continuous scale and hemosiderin (P=0.10 via t test). The number of subjects with focal stroke (n=1) or periventricular leukomalacia (n=2) was too small to determine whether any NIRS variables were associated with these specific brain lesions. With respect to the secondary NIRS variables, the average rSO2 from postinduction to 60 minutes post-CPB was lower in those subjects with hemosiderin (71±10% versus 78±6%, P=0.01 via t test). By perfusion phase, average rSO2 was lower during the rewarming phase (72±12% versus 83±9%, P=0.003) and off-CPB to 60 minutes post-CPB (65±11% versus 75±10%, P=0.009; Figure 2) in those subjects with brain hemosiderin. Similarly, minimum rSO2 was lower during the rewarming phase (61±11% versus 71±11%,

| Table 2. Intraoperative rSO2 Variables According to Categories of Integrated rSO2 ≤45% |
|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
| Variable                          | 0 min% (n=66)                     | 0.3–39 min% (n=12)               | 60–383 min% (n=11)               | P                                |
| Integrated rSO2 ≤45%, min%        | 0                                 | 17±14                            | 148±96                           | <0.001                           |
| Total duration ≤45%, min          | 0                                 | 6±6                              | 33±19                            | <0.001                           |
| Longest duration ≤45%, min        | 0                                 | 6±5                              | 20±7                             | <0.001                           |
| Postinduction to 60 min post-CPB  | Average rSO2 %                    | 79±6                             | 69±7                             | <0.001                           |
|                                   | Minimum rSO2                       | 56±7                             | 40±3                             | <0.001                           |
| Postinduction to on-CPB           | Average rSO2                       | 69±10                            | 58±6                             | <0.001                           |
|                                   | Minimum rSO2                       | 60±9                             | 44±8                             | <0.001                           |
| Onset of cooling to onset of last rewarming | Average rSO2 | 85±7                             | 79±11                            | <0.001                           |
|                                   | Minimum rSO2                       | 67±11                            | 57±13                            | <0.001                           |
| Onset of last rewarming to off-CPB| Average rSO2                       | 81±10                            | 74±11                            | 0.06                             |
|                                   | Minimum rSO2                       | 71±12                            | 61±10                            | 0.02                             |
| Off-CPB to 60 min post-CPB        | Average rSO2                       | 78±9                             | 63±9                             | <0.001                           |
|                                   | Minimum rSO2                       | 68±10                            | 54±11                            | <0.001                           |

Values are expressed as mean±SD. P values are determined by ANOVA.
and off-CPB to 60 minutes post-CPB (56±11% versus 66±12%, \(P=0.02\)) in those subjects with brain hemosiderin. There were no statistically significant differences between those subjects with and without hemosiderin in average and minimum \(rSO_2\) during the prebypass and onset of cooling to onset of first rewarming phases or with \(rSO_2\) at 10 minutes of cooling.

Next, we analyzed the relationship between NIRS data and quantitative MRI measures to determine whether specific NIRS variables predicted changes in brain volumes or white matter microstructure, adjusting for age at MRI evaluation (Table 3). NIRS variables were not strongly associated with

\[
\begin{array}{|c|c|c|c|c|}
\hline
\text{Variable} & \text{0 min\%} & \text{0.3–39 min\%} & \text{60–383 min\%} & \text{P} \\
\hline
\text{Bayley Scales of Infant Development} & n=66 & n=12 & n=11 & \\
\text{Psychomotor Development Index} & 88±16 & 85±20 & 86±17 & 0.81 \\
\text{Mental Development Index} & 94±11 & 91±17 & 96±10 & 0.41 \\
\text{Neurological examination} & n=62 & n=12 & n=10 & \\
\text{Abnormal neurological examination, n (\%)} & 37 (60) & 8 (67) & 5 (50) & 0.72 \\
\text{Head circumference, z score} & −0.02±1.04 & 0.04±0.86 & −0.16±1.10 & 0.89 \\
\text{MRI, qualitative} & n=30 & n=6 & n=4 \\
\text{Brain hemosiderin, n (\%)} & 9 (30) & 3 (50) & 2 (50) & 0.46 \\
\text{Focal stroke} & 1 (3) & 0 & 0 & 1.0 \\
\text{Periventricular leukomalacia} & 2 (7) & 0 & 0 & 1.0 \\
\text{MRI, quantitative, volume in mL} & n=30 & n=6 & n=4 \\
\text{Gray matter} & 622±62 & 606±25 & 579±55 & 0.49 \\
\text{Subcortical gray matter} & 32±11 & 35±8 & 43±9 & 0.02 \\
\text{Myelinated white matter} & 81±36 & 80±31 & 75±26 & 0.69 \\
\text{Unmyelinated white matter} & 177±41 & 184±57 & 148±27 & 0.38 \\
\text{Cerebrospinal fluid} & 99±36 & 101±29 & 79±10 & 0.57 \\
\text{Brain} & 912±94 & 906±70 & 844±99 & 0.50 \\
\text{Cerebrum} & 811±86 & 808±66 & 748±86 & 0.47 \\
\text{Cerebellum} & 101±11 & 98±9 & 96±13 & 0.87 \\
\hline
\end{array}
\]

Values are expressed as mean±SD. \(P\) values were determined by ANOVA for continuous variables and Fisher exact test for categorical variables. \(P\) values for Bayley Scales were also adjusted for social class, and \(P\) values for quantitative MRI variables were also adjusted for age at MRI evaluation.

\(P=0.006\) and off-CPB to 60 minutes post-CPB (56±11% versus 66±12%, \(P=0.02\)) in those subjects with brain hemosiderin. There were no statistically significant differences between those subjects with and without hemosiderin in average and minimum \(rSO_2\) during the prebypass and onset of cooling to onset of first rewarming phases or with \(rSO_2\) at 10 minutes of cooling.

Figure 1. Psychomotor Development Index as a function of average \(rSO_2\) from off-CPB to 60 minutes post-CPB by scatterplot. The solid line was derived by unadjusted linear regression of the data, and the dashed lines delimit the 95% confidence interval. The linear regression \(P\) value shown is for the effect of average \(rSO_2\) from off-CPB to 60 minutes post-CPB on the Psychomotor Development Index, with adjustment for social class.

Figure 2. Box plots of average \(rSO_2\) from off-CPB to 60 minutes post-CPB by hemosiderin status. A solid bar within the box represents the median value; the upper boundary of the box represents the 75th percentile and the lower boundary the 25th percentile. Vertical lines extend to the 10th and 90th percentiles, with more extreme observations plotted as filled circles. The logistic regression \(P\) value shown is for the effect on hemosiderin of average \(rSO_2\) from off-CPB to 60 minutes post-CPB.
increased subcortical gray matter volume in association with gray matter. There was an apparent paradoxical finding of gray matter volume changes, except for subcortical gray matter (P ≤ 0.05), rSO2 at 10 minutes of cooling (P = 0.07), rSO2 at off-CPB (P = 0.06), and average rSO2 from postinduction to 60 minutes post-CPB (P = 0.09). In models that adjusted for age ≤ 30 days, diagnosis group, and social class, statistical significance or trends were retained for the associations between PDI and average rSO2 for the phase off-CPB to 60 minutes post-CPB (P = 0.04), rSO2 at 60 minutes post-CPB (P = 0.05), minimum rSO2 for the phase off-CPB to 60 minutes post-CPB (P = 0.09), and rSO2 at off-CPB (P = 0.09). Additional adjustment for quartiles of intensive care unit and hospital length of stay did not alter the associations between rSO2 and PDI.

In regression analysis that adjusted for age ≤ 30 days, brain hemosiderin was significantly associated with average rSO2 for the phase off-CPB to 60 minutes post-CPB (P = 0.04) and rSO2 at off-CPB (P = 0.01; Table 5). In addition, there was a trend toward significance for average rSO2 from postinduction to 60 minutes post-CPB (P = 0.054), as well as for minimum rSO2 from off-CPB to 60 minutes post-CPB (P = 0.06). Findings were generally similar for associations between rSO2 and brain hemosiderin after adjustment for diagnosis (Table 5). Finally, because age was so highly associated with diagnosis in this small group of children, we were unable to adjust for both diagnosis and age (the logistic regression models did not converge).

Because only 23 subjects (26%) had a decline in rSO2 to ≤ 45%, analyses were also performed at threshold levels for rSO2 ≤ 50% (38 subjects) and ≤ 55% (58 subjects). No differences in PDI, MDI, neurological examination, head circumference, or MRI variables were found between groups
Ischemia outside the optical field is not necessarily associated with abnormal or deficient intracellular oxygen utilization. The leftward shift of the oxyhemoglobin dissociation curve with hypothermia and alkalosis can result in a viability-time threshold for such injury being a saturation of 35% for 2 to 3 hours at normothermia.\textsuperscript{15} Hagino et al\textsuperscript{11} found that an average tissue oxygenation index (saturation) of <55% during 2 hours of low-flow bypass at varying degrees of hypothermia in piglets was associated with both structural and functional neurological injury. In neonates undergoing the Norwood procedure, prolonged low postoperative $rSO_2$ (<45% for >180 minutes) was associated with new or worsened ischemia on early postoperative MRI.\textsuperscript{4} It is unclear whether a longer period of mild hypoxia-ischemia is more likely to cause brain injury than transient periods of worse hypoxia-ischemia. Factors that hinder the definition of threshold levels in pediatric cardiac surgery are the variability in cerebral oxygen saturation in children with congenital heart disease,\textsuperscript{24,25} less frequent use and shorter durations of deep hypothermic circulatory arrest,\textsuperscript{5,26} use of regional low-flow perfusion as an alternative to circulatory arrest,\textsuperscript{5,27} and the reduced incidence of acute clinical neurological complications after open heart operations in children.\textsuperscript{26,29} Furthermore, devices currently approved for clinical use vary in measurement accuracy\textsuperscript{30} and do not measure intracellular oxygen utilization. The leftward shift of the oxyhemoglobin dissociation curve with hypothermia and alkalosis can result in normal or increased cerebral oxygen saturation values but can be associated with abnormal or deficient intracellular oxygenation.\textsuperscript{31–34} In the present study cohort, and as reported by others, relatively high values of $rSO_2$ were achieved during pediatric hypothermic bypass.\textsuperscript{17,35–38} Thus, the prolonged periods of low cerebral oxygen saturation achieved in laboratory studies may not be seen in the clinical setting. Consequently, it will be difficult to define an intraoperative

<table>
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<tr>
<th>$rSO_2$ Predictor Variable</th>
<th>Hemoglobin (n=40*) Logistic Regression Odds Ratio ($P$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integrated $rSO_2 \leq 45%$ (min%)</td>
<td></td>
</tr>
<tr>
<td>0 min%</td>
<td>1</td>
</tr>
<tr>
<td>0.3–39</td>
<td>2.3 (0.35)</td>
</tr>
<tr>
<td>60–383</td>
<td>2.3 (0.43)</td>
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<tr>
<td>Integrated $rSO_2 \leq 45%$ (per min%)</td>
<td></td>
</tr>
<tr>
<td>Postinduction to 60 min post-CPB</td>
<td>1.01 (0.15)</td>
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<td>Average $rSO_2$, (per %)</td>
<td>0.89 (0.02)</td>
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<tr>
<td>Minimum $rSO_2$</td>
<td>0.94 (0.08)</td>
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<tr>
<td>Onset of last rewarming to off-CPB</td>
<td></td>
</tr>
<tr>
<td>Average $rSO_2$</td>
<td>0.91 (0.009)</td>
</tr>
<tr>
<td>Minimum $rSO_2$</td>
<td>0.92 (0.01)</td>
</tr>
<tr>
<td>Off-CPB to 60 min post-CPB</td>
<td></td>
</tr>
<tr>
<td>Average $rSO_2$</td>
<td>0.92 (0.02)</td>
</tr>
<tr>
<td>Minimum $rSO_2$</td>
<td>0.93 (0.03)</td>
</tr>
<tr>
<td>rSO$_2$ 10 min after cooling</td>
<td>0.96 (0.25)</td>
</tr>
<tr>
<td>rSO$_2$, Off-CPB</td>
<td>0.87 (0.003)</td>
</tr>
<tr>
<td>rSO$_2$, 60 min post-CPB</td>
<td>0.94 (0.08)</td>
</tr>
</tbody>
</table>

Logistic regression models for hemoglobin did not converge when adjusted for both age $\leq 30$ days and diagnosis group (D-transposition of the great arteries, tetralogy of Fallot, or ventricular septal defect) due to collinearity of age and diagnosis and small cell counts.

* $n=40$, except $n=39$ for off-CPB to 60 min post-CPB and 60 minutes post-CPB regressions.

## Discussion

We found a relationship between intraoperative cerebral oxygen saturation measured by NIRS and neurodevelopmental testing at 1 year of age among infants undergoing biventricular repair without aortic arch reconstruction. Lower PDI scores were associated with lower $rSO_2$ during the 60-minute period following CPB and at the time points of 10 minutes of cooling, off-CPB, and 60 minutes post-CPB. No relationship could be demonstrated between $rSO_2$ and MDI score, neurological examination, or head circumference. The finding of hemosiderin foci on qualitative MRI analysis was associated with lower average $rSO_2$ from postinduction to 60 minutes post-CPB and lower average and minimum $rSO_2$ during rewarming and during the 60-minute period following CPB. The relationship of lower $rSO_2$ with worse PDI score and brain hemosiderin on MRI suggests that periods of intraoperative and early postoperative impaired cerebral oxygen delivery may contribute to these findings.

NIRS devices measure oxygen saturation in a mixture of arterioles, capillaries, and venules in the tissue beneath the optical probe.\textsuperscript{23} Ischemia outside the optical field is not detected, and therefore, NIRS reflects regional cerebral oxygenation. Cerebral oxygenation saturation thresholds associated with central nervous system injury in pediatric cardiac surgery are under investigation but have yet to be clearly defined. Piglet studies show functional neurological impairment at a threshold saturation of 33% to 44%,\textsuperscript{18} with the
The measurement of cerebral oxygenation, hemodynamics, and algorithms may include devices capable of multisite information on the blood concentration, as well as concentration changes in oxygenated hemoglobin, deoxygenated hemoglobin, and total hemoglobin. NIRS technology constitutes a potential limitation in the study of the relationship of cerebral oxygenation to later neurological outcomes. The light source in the INVOS 5100B is 2 light-emitting diodes with a relatively wide bandwidth; in the FORE-SIGHT (CAS Medical Systems, Branford, Conn), it is 4 laser diodes with a narrower bandwidth, and in the NIRO series (Hamamatsu Photonics, Hamamatsu, Japan), which is not approved for clinical use in the United States, it is 3 laser diodes. The INVOS and FORE-SIGHT currently display only a saturation value, whereas the NIRO additionally provides information on the blood concentration, as well as concentration changes in oxygenated hemoglobin, deoxygenated hemoglobin, and total hemoglobin. NIRS technology continues to evolve, and future development of better instruments and algorithms may include devices capable of multisite measurement of cerebral oxygenation, hemodynamics, and cellular energy status (cytochrome c oxidase). Limitations of NIRS monitors notwithstanding, the modest association between lower rSO2 after 10 minutes of cooling and lower 1-year PDI score would support the previous hypotheses that cerebral oxygen availability is limited during cooling to deep hypothermia. Similar to the postoperative period after CPB with worse PDI scores and more brain MRI abnormalities are consistent with the hypothesis that the early postbypass phase is a vulnerable period for cerebral hypoxia-ischemia. Further studies are needed to determine whether NIRS-guided management in the early postoperative period can improve neurodevelopmental outcomes. Although brain hemosiderin was associated with a lower average rSO2 from postinduction to 60 minutes post-CPB and a lower average and minimum rSO2 during rewarming and during the 60-minute period after CPB, other NIRS measures were not strongly predictive of brain injury defined by MRI analysis. Periventricular leucomalacia is commonly seen in neonates after cardiac surgery but rarely detected in older infants, and higher flow rates associated with higher rSO2 may cause hyperperfusion injury to these deep brain structures. Important limitations pertain to our analyses of the relationship between NIRS levels of oxygenation and neurodevelopmental outcome and qualitative and quantitative findings on brain MRI. First, NIRS monitoring was only begun after induction of anesthesia and monitored continuously up to 1 hour post-CPB, with time-point measurements at 6 and 18 hours post-CPB, which precluded a more comprehensive evaluation of preoperative and postoperative cerebral oxygenation and outcome. Second, although 89 subjects with NIRS data returned for neurodevelopmental follow-up at 1 year of age, only 40 of those subjects underwent an MRI scan. This limited the power to detect significant associations between NIRS and MRI measures. Moreover, because age at surgery was closely correlated with diagnosis, it was not possible to determine whether diagnosis (and conduct of CPB) or age at surgery was the main factor associated with hemosiderin. Third, the power to detect associations may be limited, because a decline in rSO2 to ≤45% for a duration of at least 1 minute occurred in only 26% of subjects in the present study. Although paradoxically associated with a higher volume of subcortical gray matter, greater integrated rSO2 ≤45% was not associated with cortical gray matter, white matter, or brain volume, which suggests that the higher volume of subcortical gray matter may be an artifact of population differences in brain volume or the difficulty of accurately segmenting this small brain region. Moreover, the ability to detect tiny strokes and subtle periventricular white matter injury by MRI is diminished at 1 year of age. Thus, the low rates of stroke and white matter injury in the present cohort may underestimate the true incidence of such lesions. Fourth, during the period of the study, not all patients with tetralogy of Fallot were routinely tested for 22q11 microdeletions. Fifth, we did not correct for multiple comparisons, because the primary NIRS variable was not significantly associated with the neurodevelopmental outcomes. Because we view analyses of the secondary NIRS variables as exploratory, we similarly did not correct for multiple comparisons. Finally, the present results may not be generalizable to higher-risk populations, such as those undergoing the Norwood procedure, or to centers that use other protocols for vital organ support, such as regional perfusion. In conclusion, the present study of infants undergoing biventricular repair without aortic arch reconstruction found an association between rSO2 at early cooling and during the 60-minute period after CPB with PDI score, as well as an association between lower intraoperative rSO2 and hemosiderin foci on qualitative MRI analysis. However, our study design and the strong association among potentially explanatory variables, including neonatal age and diagnosis group, do not permit us to assess which factors are causal. Future prospective multicenter studies are needed to define NIRS thresholds of injury in the clinical setting, determine the costs and benefits of an expensive technology, and evaluate NIRS monitoring and brain imaging in various cardiac surgical populations.
of Cardiology, Ludmila Kyn for database and statistical programming; Donna M. Donati, Donna M. Duva, and Lisa-Jean Buckley for data management; and Kathleen M. Alexander for project coordination.

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Disclosures

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References

31. Dexter F, Hindman BJ. Theoretical analysis of cerebral venous blood hemoglobin oxygen saturation as an index of cerebral oxygenation during


**CLINICAL PERSPECTIVE**

This study explored whether intraoperative cerebral oxygen saturation (rSO2) measured by near-infrared spectroscopy was associated with neurodevelopmental outcomes at age 1 year among infants undergoing biventricular repair without aortic arch reconstruction. Lower Psychomotor Development Index of the Bayley Scales was modestly associated with lower rSO2 during the 60-minute period after cardiopulmonary bypass and at the time points of 10 minutes of cooling, off-cardiopulmonary bypass, and 60 minutes after cardiopulmonary bypass. Lower rSO2 from postinduction to 60 minutes after cardiopulmonary bypass and for the 60-minute period after cardiopulmonary bypass was associated with hemosiderin foci on qualitative magnetic resonance imaging analysis. No relationship could be demonstrated between rSO2 and the Mental Development Index of the Bayley Scales, neurological examination, or head circumference. The relationship of lower rSO2 with lower Psychomotor Development Index score and greater risk of hemosiderin on brain magnetic resonance imaging, even after adjustment for age ≤30 days or diagnosis group, suggests that periods of intraoperative and early postoperative decreased cerebral oxygen delivery are associated with adverse longer-term neurodevelopmental outcomes.
Relationship of Intraoperative Cerebral Oxygen Saturation to Neurodevelopmental Outcome and Brain Magnetic Resonance Imaging at 1 Year of Age in Infants Undergoing Biventricular Repair


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