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Cerebral Oximetry During Infant Cardiac Surgery: Evaluation of and Relationship to Early Postoperative Outcome

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Abstract

Background—We examined changes in cerebral oxygen saturation during infant heart surgery and its relationship to anatomic diagnosis and early outcome

Methods—Regional cerebral oxygen saturation (rSO₂) was measured by near-infrared spectroscopy in 104 infants undergoing biventricular repair without aortic arch obstruction as part of a randomized trial of hemodilution to a hematocrit of 25% versus 35%.

Results—Prior to cardiopulmonary bypass (CPB), infants with tetralogy of Fallot had higher rSO₂ values compared to those with D-transposition of the great arteries (D-TGA) or ventricular septal defect ($P < 0.001$). During CPB cooling, low flow and at the termination of CPB, D-TGA subjects had the highest rSO₂ values ($P < 0.001$). There were no significant associations between intraoperative rSO₂ and early postoperative outcomes after adjustment for diagnosis. In 39 D-TGA subjects with ≥ 5 minutes of deep hypothermic circulatory arrest, there was no correlation between the rSO₂ ($91 \pm 6\%$) or hematocrit ($29.2 \pm 5.5\%$) at the onset of arrest and the rate of decline in rSO₂ during arrest.

Conclusions—Intraoperative rSO₂ varies according to anatomic diagnosis but accounts for very little of the variance in early outcome. As measured by frontal near-infrared spectroscopy, higher levels of hematocrit and current perfusion techniques appear to provide an adequate oxygen reservoir prior to relatively short periods of deep hypothermic circulatory arrest.

Introduction

The relationship between near-infrared spectroscopic measurement of cerebral oxygenation and anatomic diagnosis on early postoperative outcome after congenital heart surgery has not been evaluated. Widespread adoption of near-infrared spectroscopy (NIRS) for neuromonitoring during cardiopulmonary bypass (CPB) has been advocated (1), based on the presumed risk of changes in brain oxygenation at distinct phases reflecting fundamental cerebral responses to hypothermic bypass, circulatory arrest and reperfusion (2). Survival piglet models of deep hypothermic circulatory arrest (DHCA) have shown that NIRS variables are influenced by hematocrit, temperature and pH strategy, and that the time to nadir and the time at the nadir of the oxyhemoglobin signal is related to neurologic outcome (3,4). Cerebral oxygenation saturation thresholds during hypoxia-ischemia in piglet models have been defined by NIRS (5), but such thresholds or nadir values have not been determined for children undergoing cardiac surgery. Differences in cerebral oxygen saturation in children with congenital heart disease before cardiac surgery have made establishment of critical thresholds more difficult (6,7). Prolonged low postoperative cerebral oxygen saturation (<45% for >180 cumulative minutes) was associated with the development of new or worsened ischemia on brain magnetic resonance imaging in a small number of neonates after the Norwood procedure for hypoplastic left heart syndrome (8). Although hematocrit has an effect on cerebral oxygenation, we have recently found little difference in cerebral oxygen saturation between hemodilution to a hematocrit of 25% versus 35% during infant heart surgery (9).

Monitoring of cerebral oxygen saturation by NIRS and using the brain as an index organ for perfusion in adult cardiac surgery has been associated with fewer incidences of major organ dysfunction and shorter duration in the intensive care unit (ICU) (10). The aim of this study was to observe changes in cerebral oxygen saturation by NIRS during infant heart surgery and to evaluate the relationship to anatomic diagnosis and early postoperative outcome.

Methods

Patients and Study Design

With IRB approval and parental informed consent, patients were enrolled between April 2001 and July 2004 at Children's Hospital Boston in a prospective randomized trial comparing early postoperative course and neurodevelopmental outcome after hemodilution to a hematocrit of 25% versus 35% during hypothermic CPB for reparative infant heart surgery (9). Eligibility criteria included reparative heart surgery at less than 9-months-of-age in 3 diagnostic groups: (1) D-transposition of the great arteries (D-TGA), (2) tetralogy of Fallot (TOF) with or without pulmonary atresia or truncus arteriosus, and (3) ventricular septal defect (VSD) or complete common atrioventricular canal defect. Exclusion criteria included birth weight <2.3 kg, recognizable phenotypic syndrome of congenital anomalies, extracardiac anomalies of more 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. Cerebral oxygen saturation monitoring was an integral part of the study protocol. Of the 124 subjects who underwent reparative surgical intervention according to the study protocol, cerebral oximetry was used in 104 patients who constitute the study population.

Anesthesia and Perfusion Methods

Anesthetic technique was not specifically controlled but was conducted according to our institutional practice. High-dose opioid anesthesia (fentanyl 100 mcg/kg) was supplemented with midazolam and/or isoflurane as tolerated, and neuromuscular blockade achieved with pancuronium. The head was turned to just off the midline to prevent pressure or movement on

the endotracheal tube by the surgical team while avoiding the possible effects of extremes of lateral head position on cerebral blood flow and venous drainage. Standard monitoring was used, including a radial or femoral artery catheter for measurement of systemic arterial blood pressure and intermittent blood sampling.

After induction of anesthesia and placement of an arterial catheter, surface cooling was initiated with low ambient room temperature, a cooling mattress and ice packs to the head. Core cooling was begun with the initiation of CPB. The bypass circuit was primed with whole blood and Plasma-lyte A pH 7.4 (Multiple Electrolytes Injection, Type 1, USP), with the aim of obtaining a hematocrit of 25% or 35% at the time of onset of low-flow CPB. A nonpulsatile roller pump with a membrane oxygenator (D 901 Lilliput 1 Open System, Dideco, Mirandola, Italy) was used. The pH-stat strategy was used during core cooling, low-flow hypothermic perfusion and rewarming up to 30°C. Patients had variable periods of full-flow CPB at approximately 2.5 L·min⁻¹·m⁻² when cooling to various levels of hypothermia and usually during rewarming. Some patients had periods of DHCA, and most had at least 1 period of reduced-flow CPB (low-flow CPB), e.g., at approximately 0.75 L·min⁻¹·m⁻² when at deep hypothermia (rectal temperature <18°C). Methylprednisolone (30 mg/kg), phentolamine (0.2 mg/kg) and furosemide (0.25 mg/kg) were given at the initiation of CPB to all patients. At the onset of rewarming, mannitol (0.5 g/kg) and phentolamine (0.2 mg/kg) were given to all patients. Patients were rewarmed for at least 30 minutes and to a rectal temperature of 34°C. Conventional ultrafiltration was used during CPB, but not modified ultrafiltration after CPB.

Monitoring and Data Acquisition

Regional cerebral oxygen saturation (rSO₂) was measured with the INVOS 5100B (Somanetics, Troy, MI). The INVOS 5100B is a continuous wave spectrometer that uses 2 wavelengths of near-infrared light (730 and 805 nm) to measure the ratio of oxyhemoglobin to total hemoglobin. The resultant cerebral oxygen saturation is expressed as the rSO₂, the scale unit of which is percent (%). After induction of anesthesia, Pediatric SomaSensors® (Somanetics, Troy, MI) were placed on the right and left forehead according to the manufacturer's guidelines. After an accommodation period, data collection was begun and downloaded to storage disk every 10 seconds throughout the case for further analysis.

Intraoperative and early postoperative data were collected and analyzed at the following time points: postinduction, at heparin administration, initiation of CPB (onset of cooling), 10 minutes after start of cooling, onset of low-flow bypass, onset of DHCA, resumption of low-flow CPB, start of rewarming, 10 minutes after start of rewarming, warm flow (35°C), immediately off CPB, and 60 minutes, 6 hours and 18 hours post-CPB. Postoperative data included serum lactate levels, cardiac output by thermodilution technique (11), laboratory studies (hematocrit, arterial blood gas, mixed venous oxygen saturation), events, and length of intubation, ICU and hospital stay.

NIRS and Outcome Measurements

Analysis of the first 62 patients found rSO₂ measurements from the left and right cerebral hemispheres to be similar (12). Consequently, an average of the left and right rSO₂ [(left plus right rSO₂)/2] was used for data analysis. Because rSO₂ is close to jugular bulb oxygen saturation (13), cerebral oxygen extraction (CEO₂) can be estimated from the difference of arterial oxygen saturation (SaO₂) and rSO₂ (CEO₂ = SaO₂ - rSO₂). In addition to the rSO₂ at each time point, the following intraoperative NIRS variables were used for correlation analysis to assess the critical phases of CPB: average rSO₂ and minimum rSO₂ (defined as the lowest 1-minute average rSO₂) for the time period postinduction to 60 minutes post-CPB, postinduction to on CPB, onset cooling to onset last rewarming, onset last rewarming to off CPB and off CPB to 60 minutes post-CPB. Based on laboratory and clinical studies (5,8), an

rSO₂ of 45% was chosen as the threshold value for determining the relationship of a cerebral oxygen saturation threshold to early postoperative outcome. The total duration and longest duration of rSO₂ ≤45% (minutes) and the integrated rSO₂ ≤45% (minutes*desaturation points ≤45% or area under the curve (AUC)) were used for the analysis. The 1-minute average criterion was used to identify those subjects who had a decline in rSO₂ to ≤45%. Comparisons were then done between those subjects in whom the rSO₂ did not decrease to ≤45% (AUC = 0 min%) and 2 groups of subjects dichotomized by the median of the integrated rSO₂ ≤45%. Because there may be a nonlinear relationship between rSO₂ and early outcome, similar analyses were done using 50%, 55% and 60% as possible threshold values. We assessed possible associations between intraoperative rSO₂ and the following outcome measurements: lactate at 60 minutes post-CPB, cardiac index at 6 and 18 hours post CPB, length of intubation, ICU and hospital stay, and Modified Pediatric Risk of Mortality-III (PRISM III) scores at 12 and 24 hours post-CPB (14).

Statistical Analysis

Comparisons of perioperative variables and NIRS values across the 3 diagnostic groups were made using Fisher's exact test for categorical variables and analysis of variance for continuous variables. Comparisons of outcomes in subjects whose rSO₂ remained above 45% versus those in whom rSO₂ decreased to ≤45% were made using equal variance *t*-tests, with Wilcoxon rank sum tests used for hospital course variables due to their skewness. To assess associations between NIRS variables and continuous outcomes, Spearman rank correlation coefficients were used. To adjust for possible confounding or effect modification by diagnostic group, Spearman rank correlation coefficients, stratified by diagnostic group, and linear regression, adjusting for diagnostic group, were used. In this secondary analysis of data arising from a clinical trial, a sample size of 104 subjects provides 90% power to detect correlations of 0.31 or larger, and 80% power to detect correlations of 0.27 or larger, in a 2-sided 0.05 level test of the null hypothesis of no correlation between NIRS variables and continuous outcomes.

Nonlinear regression modeling was used to fit the decline in mean rSO₂ across subjects during circulatory arrest, among subjects with D-TGA who had ≥5 minutes of DHCA. We fit an exponential decay curve, namely

$$\text{mean rSO}_2 = \beta_0 - \beta_1 [1 - \exp(-\beta_2 \times \text{time})],$$

where β_0 represents the fitted value of mean rSO₂ at the start of DHCA, β_1 represents the asymptotic decline in mean rSO₂ for a long period of DHCA, β_2 relates to the exponential rate of decline, and time is the duration of DHCA, in minutes. This model was fit via PROC NLIN in SAS Version 9.1.3 (SAS Institute Inc., Cary, NC) using minute-by-minute averaged rSO₂ values across subjects, with weighting proportional to the number of subjects contributing data at that time point. Due to the small number of subjects with DHCA duration >30 minutes, we limited this analysis to between 0–30 minutes of DHCA. Based on previous work (3), we estimated the time to NIRS nadir as the estimated time beyond which the slope, or decay, remains <0.5 % per minute, here equal to $[\ln(2 \times \beta_1 \times \beta_2)] / \beta_2$.

Results

Of 124 infants enrolled in the primary study, 104 (84%) had NIRS monitoring of cerebral oxygenation. One family declined the NIRS component, and neuromonitoring personnel were not available for 19 subjects. Analysis of perioperative variables showed no differences in those patients who had NIRS monitoring versus those who did not. All patients survived to discharge, and none developed clinical seizures, stroke or choreoathetosis.

Demographic and operative characteristics and early outcome variables according to diagnosis group are shown in Table 1. Patients with D-TGA were younger, more likely to be mechanically ventilated prior to surgery, had longer durations of total CPB, low-flow bypass, circulatory arrest, total support (i.e., total CPB time plus circulatory arrest time) and crossclamp time and had a more demanding postoperative course. Duration of cooling was similar for all groups.

Changes in Cerebral Oxygen Saturation

Physiologic data, rSO_2 and CEO_2 at each time point by diagnostic group are shown in Table 2, Table 3, and Table 4, respectively. The TOF group had the highest rSO_2 and the lowest CEO_2 after induction of anesthesia and prior to CPB ($P < 0.001$). During CPB, rSO_2 was significantly higher in the D-TGA group at 10 minutes after cooling, onset low-flow bypass, at warm flow and after separation from bypass ($P < 0.001$). D-TGA patients had lower temperatures and higher arterial carbon-dioxide ($PaCO_2$) tensions during bypass; mean arterial blood pressure was lower but there was no difference in hematocrit. Ninety-five percent of D-TGA patients underwent DHCA, more than in the other groups ($P < 0.001$). The D-TGA group had the highest rSO_2 and lowest CEO_2 at the end of bypass ($P < 0.001$), but there were no differences among the groups in the immediate post-bypass period. At 18 hours after cessation of CPB, the D-TGA group had the highest rSO_2 ($P < 0.001$) and the lowest CEO_2 ($P < 0.001$).

Analysis of rSO_2 as a continuous variable from postinduction to 60 minutes post CPB, with examination by operative phase, is shown in Table 5. The mean average rSO_2 was highest in the D-TGA group and lowest in the VSD group ($P < 0.001$), but there was no diagnosis group difference in the mean minimum rSO_2 . TOF was associated with the highest average rSO_2 during the pre-bypass phase, while average rSO_2 was highest in the D-TGA group during hypothermic bypass, rewarming and the first hour after CPB. The rSO_2 declined to $\leq 45\%$ in 23 infants (22%), with no difference among diagnosis groups in the incidence, total and longest duration $\leq 45\%$ or in the integrated rSO_2 (AUC) $\leq 45\%$.

Relationship of NIRS to Early Postoperative Outcome

As no patient in this study died or developed clinical seizures, stroke or choreoathetosis, the relationship between intraoperative NIRS variables and early clinical neurologic outcome could not be determined. Correlation matrices and regression analysis using the NIRS variables average and minimum rSO_2 for the period postinduction to 60 minutes post-CPB, as well as the average and minimum rSO_2 for each operative phase (as presented in Table 5), total and longest duration of $rSO_2 \leq 45\%$ and integrated $rSO_2 \leq 45\%$, found no statistically or clinically significant associations between cerebral oxygen saturation and lactate at 60 minutes post-CPB, cardiac index at 6 and 18 hours post-CPB, PRISM III scores, and length of intubation, ICU and hospital stay. The lack of association between NIRS and early postoperative outcome was found for the entire cohort as well as within each diagnosis group. A plot relating the AUC for $rSO_2 \leq 45\%$ to days in the ICU is shown in Figure 1, and is representative of the lack of a clear pattern between intraoperative NIRS and early outcome. Area under the curve analysis found no difference in early outcome variables between those subjects in whom the rSO_2 remained above 45% versus those in whom the rSO_2 decreased to $\leq 45\%$ (Table 6). Analyses using threshold values of 50%, 55% and 60% similarly found no relationship to early outcome (data not presented).

Early outcomes were not significantly associated with rSO_2 at 60 minutes, 6 hours, or 18 hours post-CPB. Lower CEO_2 at 18 hours post-CPB was correlated with prolonged days intubated and ICU stay, and higher PRISM III scores at 24 hours postoperatively, but this correlation was no longer present with adjustment for diagnosis (linear regression). Although the TGA group had the lowest CEO_2 at 18 hours post-CPB, within the TGA subjects this was not related to poorer outcome.

DHCA

Change in rSO₂ during DHCA was analyzed in the homogenous group of D-TGA subjects who had ≥5 minutes of arrest (n = 39). Mean duration of the longest cycle of circulatory arrest was 20 ± 11 minutes, with a median (range) of 19 (5 – 58) minutes. Mean duration of cooling prior to circulatory arrest was 19 ± 9 minutes. Mean rSO₂ at the onset of arrest was 91 ± 6%, with a median (range) of 94 (70 – 95)%. The change in mean rSO₂ was -12 ± 6 (mean ± standard deviation), -17 ± 7, -22 ± 8, -27 ± 8, -31 ± 10, and -43 ± 9% at 5, 10, 15, 20, 25, and 30 minutes of arrest, respectively (Figure 2). The change in mean rSO₂ at 30 minutes of arrest was based on only 4 subjects. In individual patients, the rate of decline in rSO₂ during arrest was not correlated with the rSO₂ value at the onset of arrest. No correlation was found between the hematocrit at the onset of low-flow bypass prior to arrest (29.2 ± 5.5%) and the rSO₂ value at the onset of arrest or rate of decline during arrest. There was no difference in the rate of decline in rSO₂ between those TGA subjects with an intact ventricular septum (n = 20) versus those with a VSD (n = 19) who had ≥ 5 minutes of arrest. By visual inspection of the graphical display of the decline in rSO₂ during DHCA for each subject, no patient reached a nadir (plateau) rSO₂ by 25 minutes of arrest (n = 15). Although 1 patient appeared to reach a nadir by 58 minutes of arrest, the number of subjects with more than 25 minutes of arrest was too small to precisely determine when a nadir rSO₂ would be reached.

The nonlinear exponential decay model (plotted in Figure 2) estimated β_0 as 88.6 ± 0.6 (mean ± standard error) for the fitted value of mean rSO₂ at the start of DHCA, β_1 as 53.8 ± 6.6 for the fitted asymptotic decline in mean rSO₂ for a long period of DHCA, and β_2 as 0.034 ± 0.006 for the exponential rate of decline parameter. If the nadir was defined as the time at which the slope of the fitted nonlinear curve was <0.5 % (scale units) for a 1-minute average rSO₂ (3), the nadir would be estimated to be 38 minutes. However, this estimate should be viewed with caution as it is an extrapolation beyond the range of the data used in the fitting of the model and only 2 D-TGA subjects were observed with >38 minutes of arrest.

Discussion

We found that intraoperative cerebral oxygen saturation in a series of infants undergoing biventricular repair varies according to diagnosis and was not associated with early hemodynamic and clinical outcome. The relationship between intraoperative NIRS variables and early clinical neurologic outcome could not be determined, as no subject in this cohort died or developed clinical seizures, stroke or choreoathetosis.

Cerebral oxygen saturation before congenital heart surgery varies with anatomy and arterial saturation, as well as within diagnosis groups (6,7). Saturation values from different NIRS instruments are not identical (15–17) as monitors use different spectroscopic techniques (continuous-wave, frequency-domain or time-domain) to measure cerebral oxygen saturation (18). Nevertheless, the higher values in the TOF patients and, to a lesser extent, in the D-TGA patients after induction of anesthesia can be explained by the increased arterial SaO₂ associated with use of increased inspired oxygen concentrations and the decrease in oxygen consumption during anesthesia (resulting in a higher cerebral venous oxygen saturation). The use of the highest inspired oxygen concentrations in the TOF group likely accounts for the greatest rSO₂ values prebypass. In contrast to preoperatively, the VSD group had a similar rSO₂ but with an increased CEO₂ postinduction; because physiologic variables (SaO₂, PaO₂, hematocrit) were similar to the TOF group, this may have been due to a less favorable systemic to pulmonary blood flow ratio. Techniques of CPB, namely the lower temperature, increased arterial carbon-dioxide tension, and greater use of DHCA in the D-TGA patients, likely account for the differences in cerebral oxygen saturation during bypass (19–21). As cerebral oxygen saturation reflects differences in anatomy and physiology of lesions and associated management techniques, diagnosis is collinear with cerebral oxygen saturation and should be

considered when relating NIRS values to outcome. In other words, diagnosis will dictate the management strategy and thereby influence cerebral oxygen saturation.

The high rSO_2 values seen during hypothermic bypass in this study could affect the rate of decline to a critical threshold, as well as the cumulative time spent below such a value. Although 23 patients (22%) had a decline in rSO_2 to $\leq 45\%$, a level associated with functional impairment in an animal model (5) and ischemia on brain magnetic resonance imaging in neonates (8), the extremely brief periods of desaturation at these levels combined with limited statistical power in a cohort with a low expectation of adverse outcome precluded demonstration of a significant relationship to early outcome. This study was thus not able to define a critical threshold level that relates to early postoperative outcome in a homogeneous and relatively straightforward cardiac surgical population. Cerebral oxygen saturation measured by NIRS during coronary bypass surgery has been used as a surrogate for systemic tissue perfusion (10), so that the relationship to early outcome may be different with more complex congenital anomalies such as Norwood procedures or repair of complex interrupted aortic arch.

Laboratory studies in piglet models of DHCA using NIRS have demonstrated that higher temperature, lower hematocrit, more alkaline pH and longer duration of circulatory arrest are predictive of more severe damage to the brain (3,4). Higher hematocrit is thought to be advantageous at the onset of circulatory arrest because of an increased reservoir of oxygen from which the brain can draw throughout the period of arrest. In the primary study from which our cohort is derived, there were no differences in cerebral oxygen saturation at the onset of DHCA or at resumption of low flow bypass between those infants with a hematocrit of 25% versus 35% (9). In the 39 neonates with D-TGA who had ≥ 5 minutes of DHCA, we found that the rate of decline in cerebral oxygen saturation was not related to the hematocrit at the onset of low-flow bypass prior to arrest. Assuming that the frontal NIRS tracks well with global cerebral oxygen saturation values, and with current perfusion techniques (pH-stat strategy and slow cooling to deep hypothermia), this finding implies that there is little to gain in increasing the size of the oxygen reservoir at the onset of DHCA by further increases in hematocrit. Kurth et al. showed that in neonates with an α -stat blood gas strategy and a hematocrit of 25% during 12 minutes of cooling, cerebral oxygen saturation decreased curvilinearly for 40 minutes during DHCA, but did not change thereafter (2). In the present study, with a pH-stat strategy, higher mean hematocrit, longer duration of cooling and shorter arrest periods, no subject reached a nadir rSO_2 at 25 minutes of arrest. The number of subjects with more than 25 minutes of arrest was too small to precisely determine when a nadir rSO_2 would be reached. The nonlinear exponential decay model estimated a nadir rSO_2 at 38 minutes of arrest, but this estimate should be viewed with caution, as it is an extrapolation beyond the range of the data used in the fitting of the model (data up to 30 minutes of arrest used) and only 2 D-TGA subjects were observed with more than 38 minutes of arrest. The abrupt change in the slope of the data-curve between 25 and 30 minutes of arrest is likely due to the resumption of CPB and thus dropping out of those subjects with higher mean rSO_2 values.

Shorter durations and less frequent use of circulatory arrest over the past decade may limit the use of laboratory-derived NIRS variables in the clinical setting. The time at the nadir of the oxygenated hemoglobin signal has been correlated with brain damage after 60 to 100 minutes of DHCA in a piglet model (3). In our study, the median (range) duration of DHCA in the 39 neonates with D-TGA who had ≥ 5 minutes of arrest was 19 (5 – 58) minutes. During 2 hours of low flow bypass in piglets, an average tissue oxygenation index of less than 55% was associated with structural and functional neurologic injury (22). Durations of low flow bypass were much less than 2 hours in the majority of our patients (upper quartile 64.5 minutes) and were associated with rSO_2 values above 55%. The risk of neurologic injury related to DHCA in our cohort was likely to be low.

NIRS provides a constant measuring tool of cerebral oxygenation, but threshold levels associated with central nervous system injury in pediatric cardiac surgery are still undefined. Whereas a randomized, prospective intervention study of cerebral oximetry in adults found significantly fewer incidences of major organ dysfunction with treatment of declining rSO_2 (10), such a study has not been performed in children. The decreased incidence of acute neurologic complications after open-heart operations in children (23,24) makes it more difficult to relate intraoperative changes in NIRS to early neurologic outcome (25). As no subject in the present study developed clinical seizures, stroke or choreoathetosis, it was not possible to determine the relationship between intraoperative NIRS variables and early clinical neurologic outcome.

Although lower CEO_2 at 18 hours post-CPB was correlated with some early outcome variables for the entire cohort, this relationship was no longer present with adjustment for diagnosis. The lowest CEO_2 at 18 hours post-CPB found in the TGA group probably reflects management strategies in our cardiac ICU regarding anticipated duration of mechanical ventilation and recovery. We evaluated correlations between rSO_2 and outcomes for the entire cohort and found no statistical or clinical significance within diagnostic groups (Spearman correlation). Similarly, regression methods adjusting for diagnostic group did not show any statistically significant effects of any NIRS variable on early outcome. The representative figure illustrates the relationship between integrated $rSO_2 \leq 45\%$ and days in ICU. Plots demonstrating the relationship of other NIRS variables to the early outcome variables for the study population appear similar.

Our study population of infants undergoing biventricular repair without aortic arch obstruction limits the generalizability of the findings to other cardiac lesions. The single-center design and perfusion strategy also need to be considered. The randomized, prospective interventional study, considered the “gold standard,” is very difficult to perform in this patient population. Difficulties include the need for a large cohort, the many variables that need to be controlled, varying baseline saturations with many below the expected normal range, defining thresholds for intervention (particularly with “abnormal” baselines), the higher intraoperative cerebral oxygen saturation levels seen in young patients and the ethical issues (1). The relatively short duration of DHCA and small sample size limited the ability of this study to determine a nadir rSO_2 during circulatory arrest and its application to early outcome.

In summary, this analysis of intraoperative cerebral oxygen saturation in infants undergoing biventricular repair without aortic arch obstruction varied according to diagnosis and, within the range of variability observed, failed to demonstrate a relationship to early postoperative outcome. With relatively high hematocrit, slow cooling to deep hypothermia and a pH-stat strategy, the rate of decline in cerebral oxygen saturation during DHCA in neonates with D-TGA was not related to the hematocrit at the onset of arrest and no patient reached a saturation plateau at 25 minutes of arrest. Evaluation of intraoperative cerebral oxygen saturation in relation to neurodevelopmental outcome in this cohort is continuing.

Implications Statement

We evaluated changes in cerebral oxygen saturation during reparative infant heart surgery. Intraoperative cerebral oxygen saturation varies according to anatomic diagnosis but accounts for very little of the variance in early hemodynamic and clinical outcome after biventricular repair.

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Figure 1.

Relationship of integrated regional cerebral oxygen saturation ($rSO_2 \leq 45\%$ (minutes*desaturation points $\leq 45\%$)) to days in intensive care unit (ICU). A box plot is presented for subjects whose rSO_2 remained above 45%. A solid bar within the box represents the median value, the upper boundary of the box represents the 75th percentile, and the lower boundary of the box represents the 25th percentile. The vertical lines extend to the 10th and 90th percentiles, with more extreme observations plotted as filled circles. A scatter plot is presented for subjects who had an integrated $rSO_2 \leq 45\%$. The Spearman rank correlation coefficient is denoted by r .

Figure 2.

Pattern of cerebral oxygen saturation (rSO₂) during deep hypothermic circulatory arrest (DHCA) in 39 infants with D-transposition of the great arteries who underwent ≥5 minutes of arrest. Data are presented as mean ± 1.96 SE. The number of subjects (N) available for analysis at 5-minute intervals of arrest is shown. The fitted nonlinear exponential decay curve (solid line) is based on data from 0 to 30 minutes with higher weight given to mean rSO₂ values calculated with more subjects. The fit is extrapolated beyond 30 minutes with a dashed line.

Table 1

Preoperative and Operative Characteristics and Early Outcome Variables According to Diagnosis Group

Variable	TGA (N=43)	TOF (N=36)	VSD (N=25)	P
Preoperative Characteristics				
Birth weight (kg)	3.5 ± 0.5	3.4 ± 0.5	3.5 ± 0.5	0.27
Gestational age (wk)	39.0 ± 1.5	39.3 ± 1.1	39.4 ± 1.3	0.40
Age at surgery (days), median (range)	5 (2–23)	66 (2–210)	101 (11–263)	<0.001
Sex (% male)	65	58	56	0.74
Race (% non-white)	19	25	20	0.79
Intubated at surgery (%)	26	3	0	<0.001
Operative Characteristics				
Crossclamp time (min)	95 ± 22	49 ± 11	48 ± 11	<0.001
Total support time (min)	145 ± 34	84 ± 15	80 ± 17	<0.001
Total bypass time (min)	125 ± 31	82 ± 14	76 ± 18	<0.001
Low-flow bypass time (min)	70 ± 23	34 ± 16	33 ± 18	<0.001
Duration of cooling (min)	19 ± 9	20 ± 13	17 ± 12	0.55
Nadir temperature (°C)	16 ± 2	23 ± 5	25 ± 4	<0.001
Duration of DHCA (min), median range)	18 (0–59)	0 (0–31)	0 (0–42)	<0.001
0 min (n)	2	32	23	<0.001
1–4	2	0	0	
5–30	33	3	0	
31–44	5	1	2	
≥ 45	1	0	0	
Early Outcome Variables				
Lactate 60 min post-CPB	1.9 ± 1.0	1.2 ± 0.7	0.9 ± 0.4	<0.001
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)				
6 h postoperative	3.9 ± 0.9 (n=10)	4.1 ± 1.2 (n=14)	4.6 ± 1.0 (n=9)	0.37
18 h postoperative	4.2 ± 1.3 (n=9)	4.3 ± 1.2 (n=13)	5.5 ± 1.2 (n=9)	0.06
PRISM III Score				
12 h postoperative	7.3 ± 3.2	5.2 ± 3.7	3.2 ± 2.7	<0.001
24 h postoperative	9.0 ± 3.8	7.1 ± 4.5	5.0 ± 2.6	<0.001
Days intubated, median (interquartile range)	2.1 (1.6–3.7)	1.7 (1.1–2.8)	1.1 (0.9–1.3)	<0.001
Days in intensive care unit	4 (3–5)	3 (2–4)	2 (2–3)	<0.001
Days in hospital	8 (7–9)	7 (5–8)	5 (4–6)	<0.001

Values are expressed as mean ± standard deviation. *P* values are determined by analysis of variance for continuous variables, Fisher's exact test for categorical variables, and Kruskal-Wallis tests for hospital course variables.

TGA = D-transposition of the great arteries; TOF = tetralogy of Fallot; VSD = ventricular septal defect; DHCA = deep hypothermic circulatory arrest; CPB = cardiopulmonary bypass; PRISM III = Pediatric Risk of Mortality III

Table 2

Intra- and Postoperative Physiologic Data at Each Time Point According to Diagnosis Group

Variable	TGA (N=43)	TOF (N=36)	VSD (N=25)	P
Mean Arterial Pressure (mmHg)				
Postinduction	55 ± 12	61 ± 14	61 ± 10	0.11
Heparin administration	47 ± 10	50 ± 11	50 ± 8	0.28
10 min after cooling	30 ± 9	37 ± 10	39 ± 8	<0.001
Onset of LF	22 ± 7	32 ± 12	37 ± 6	<0.001
10 min into last rewarming	35 ± 10	40 ± 9	40 ± 9	0.03
Warm flow	44 ± 10	50 ± 11	47 ± 12	0.08
60 min post CPB	56 ± 7	57 ± 9	65 ± 10	<0.001
6 h post CPB	55 ± 9	62 ± 10	64 ± 10	0.001
18 h post CPB	54 ± 7	62 ± 11	68 ± 12	<0.001
Temperature (tympanic, °C)				
Onset of LF	17.9 ± 2.6	23.6 ± 4.5	26.1 ± 3.0	<0.001
10 min into last rewarming	25.6 ± 3.4	29.9 ± 2.9	30.4 ± 3.6	<0.001
Warm flow	34.1 ± 1.6	34.4 ± 1.4	34.9 ± 0.7	0.08
60 min post CPB	34.8 ± 1.4	35.2 ± 0.9	35.6 ± 0.9	0.02
Hematocrit (%)				
Postinduction	40.9 ± 5.5	31.0 ± 4.8	31.5 ± 2.2	<0.001
Heparin administration	38.4 ± 5.2	30.2 ± 4.6	31.4 ± 2.4	<0.001
10 min after cooling	28.9 ± 5.5	28.4 ± 4.2	30.4 ± 5.1	0.31
Onset of LF	29.0 ± 5.5	28.2 ± 5.2	30.3 ± 4.6	0.29
10 min into last rewarming	33.3 ± 2.9	31.6 ± 3.8	32.3 ± 2.3	0.07
Warm flow	34.9 ± 2.5	33.6 ± 3.6	33.5 ± 2.5	0.08
60 min post-CPB	36.1 ± 4.2	36.6 ± 4.5	35.8 ± 3.6	0.77
SaO₂ (%)				
Preoperative	<0.001	93 ± 7	98 ± 3	<0.001
Postinduction	<0.001	97 ± 4	98 ± 3	<0.001
Heparin administration	0.31	95 ± 6	99 ± 2	<0.001
10 min after cooling	0.29	100 ± 0	100 ± 0	0.50
Onset of LF	0.07	100 ± 0	100 ± 0	0.53
10 min into last rewarming	0.08	99 ± 7	100 ± 1	0.46
Warm flow	0.77	100 ± 0	99 ± 6	0.09
60 min post-CPB	99 ± 3	99 ± 5	100 ± 1	0.57
6 h post-CPB	99 ± 0	98 ± 2	99 ± 1	0.04
18 h post-CPB	99 ± 1	98 ± 2	99 ± 1	0.08
PaO₂ (mmHg)				
Postinduction	71 ± 35	217 ± 160	204 ± 130	<0.001
Heparin administration	60 ± 26	185 ± 165	252 ± 159	<0.001
10 min after cooling	791 ± 22	718 ± 77	690 ± 72	<0.001
Onset of LF	790 ± 38	705 ± 83	699 ± 53	<0.001
10 min into last rewarming	526 ± 115	509 ± 115	459 ± 123	0.09
Warm flow	506 ± 86	487 ± 84	420 ± 137	0.005
60 min post CPB	286 ± 149	256 ± 148	275 ± 133	0.66
6 h post CPB	132 ± 50	111 ± 56	150 ± 43	0.02
18 h post CPB	113 ± 33	84 ± 29	113 ± 29	<0.001
PaCO₂ (mmHg)				
Postinduction	40 ± 8	42 ± 10	42 ± 12	0.68
Heparin administration	44 ± 8	47 ± 14	39 ± 8	0.03
10 min after cooling	79 ± 13	66 ± 14	66 ± 9	<0.001
Onset of LF	84 ± 14	65 ± 16	67 ± 11	<0.001
10 min into last rewarming	49 ± 14	42 ± 7	42 ± 10	0.004
Warm flow	35 ± 6	37 ± 5	40 ± 5	0.003
60 min post	43 ± 8	44 ± 9	42 ± 8	0.74
6 h post	38 ± 6	41 ± 6	40 ± 6	0.22
18 h post	41 ± 4	41 ± 5	43 ± 5	0.19

Values are expressed as mean ± standard deviation. *P* values are determined by analysis of variance.

TGA = D-transposition of the great arteries; TOF = tetralogy of Fallot; VSD = ventricular septal defect; LF = low-flow bypass; CPB = cardiopulmonary bypass; SaO₂ = arterial oxygen saturation; PaCO₂ = arterial partial pressure of carbon dioxide

Table 3Regional Cerebral Oxygen Saturation (rSO₂, %) at Each Time Point According to Diagnosis Group

Variable	TGA (N=43)	TOF (N=36)	VSD (N=25)	<i>P</i>
Postinduction	61 ± 11	71 ± 14	62 ± 9	<0.001
Heparin administration	61 ± 12	71 ± 11	63 ± 9	<0.001
On CPB	62 ± 13	67 ± 12	62 ± 12	0.12
10 min after cooling	90 ± 7	85 ± 9	81 ± 9	<0.001
Onset of LF	90 ± 7	83 ± 10	81 ± 10	<0.001
Onset of DHCA	91 ± 6	84 ± 16	90 ± 2	–
Resume LF	68 ± 15 (n=41)	64 ± 12 (n=4)	51 ± 13 (n=2)	–
Start rewarming	85 ± 12	82 ± 12	82 ± 11	0.46
Warm flow (35°C)	86 ± 7	71 ± 11	68 ± 11	<0.001
Off CPB	81 ± 10	70 ± 11	66 ± 10	<0.001
60 min post-CPB	75 ± 12	71 ± 11	71 ± 13	0.26
6 h post-CPB	64 ± 10	63 ± 9	63 ± 6	0.85
18 h post-CPB	76 ± 7	68 ± 9	71 ± 6	<0.001

Values are expressed as mean ± standard deviation. *P* values are determined by analysis of variance.

TGA = D-transposition of the great arteries; TOF = tetralogy of Fallot; VSD = ventricular septal defect; CPB = cardiopulmonary bypass; LF = low-flow bypass; DHCA = deep hypothermic circulatory arrest

Table 4Cerebral Oxygen Extraction (CEO₂, %) at Each Time Point According to Diagnosis Group

Variable	TGA (N=43)	TOF (N=36)	VSD (N=25)	<i>P</i>
Postinduction	31 ± 10	26 ± 13	37 ± 9	<0.001
Heparin administration	26 ± 10	24 ± 12	34 ± 9	<0.001
10 min after cooling	10 ± 7	15 ± 9	19 ± 9	<0.001
Onset of LF	10 ± 7	17 ± 10	18 ± 10	<0.001
10 min into last rewarming	8 ± 6	26 ± 14	31 ± 11	<0.001
Warm flow (35°C)	14 ± 7	29 ± 11	31 ± 11	<0.001
Off CPB	18 ± 9	29 ± 11	33 ± 10	<0.001
60 min post-CPB	23 ± 13	27 ± 13	29 ± 13	0.12
6 h post-CPB	32 ± 14	33 ± 12	36 ± 7	0.53
18 h post-CPB	20 ± 10	29 ± 11	28 ± 7	<0.001

Values are expressed as mean ± standard deviation. *P* values are determined by analysis of variance.

CEO₂ = SaO₂ – rSO₂; SaO₂ = arterial oxygen saturation; rSO₂ = regional cerebral oxygen saturation; TGA = D-transposition of the great arteries; TOF = tetralogy of Fallot; VSD = ventricular septal defect; LF = low flow bypass; CPB = cardiopulmonary bypass

Table 5Regional Cerebral Oxygen Saturation (rSO₂, %) According to Diagnosis Group

Variable	TGA (N=43)	TOF (N=36)	VSD (N=25)	<i>P</i>
Average rSO₂	80 ± 7	76 ± 8	71 ± 8	<0.001
Postinduction – on CPB	63 ± 10	71 ± 12	62 ± 8	<0.001
Onset cooling – onset last rewarming	85 ± 8	82 ± 9	80 ± 10	0.03
Onset last rewarming – off CPB	88 ± 6	75 ± 11	71 ± 9	<0.001
Off CPB – 60 min post-CPB	78 ± 11	73 ± 10	71 ± 11	0.02
Minimum rSO₂	51 ± 12	54 ± 10	50 ± 9	0.28
Postinduction – on CPB	54 ± 11	60 ± 13	53 ± 9	0.04
Onset cooling – onset last rewarming	60 ± 14	69 ± 12	61 ± 14	0.005
Onset last rewarming – off CPB	77 ± 9	64 ± 11	61 ± 9	<0.001
Off CPB – 60 min post-CPB	69 ± 13	62 ± 11	59 ± 10	0.004
Decline in rSO₂ ≤ 45%, n (%)	9 (21)	6 (17)	8 (32)	0.39
Total duration ≤ 45% (min)	23 (2–64)	9 (1–18)	12 (1–72)	0.10
Longest duration ≤ 45% (min)	19 (2–32)	8 (1–15)	12 (1–27)	0.12
Integrated rSO ₂ ≤ 45% (min%)	130 ± 117	28 ± 22	61 ± 75	0.12

Values are expressed as mean ± standard deviation or median (range). *P* values are determined by analysis of variance for average and minimum rSO₂ values, Fisher's exact test for decline in rSO₂ ≤ 45%, and Kruskal-Wallis tests for duration and integrated rSO₂ deviation ≤ 45% variables. Duration and integrated rSO₂ ≤ 45% variables are restricted to the 23 subjects with a decline in rSO₂ ≤ 45%.

TGA = D-transposition of the great arteries; TOF = tetralogy of Fallot; VSD = ventricular septal defect; CPB = cardiopulmonary bypass

Table 6Comparison of Early Outcome Variables by Integrated Regional Cerebral Oxygen Saturation (rSO_2) $\leq 45\%$

Variable	Integrated $\text{rSO}_2 \leq 45\%$ (min%)			<i>P</i>
	0 (N=81)	0.3–39 (N=12)	60–383 (N=11)	
Diagnostic group, n (%)				0.09
TGA	34 (42)	2 (17)	7 (64)	
TOF	30 (37)	5 (42)	1 (9)	
VSD	17 (21)	5 (42)	3 (27)	
Lactate 60 min post-CPB	2.8 $\pm$ 1.5	2.3 $\pm$ 1.4	3.5 $\pm$ 1.5	0.19
Cardiac index ($\text{L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$)				
6h postoperative	4.1 $\pm$ 1.1 (27)	4.5 $\pm$ 0.1 (2)	4.2 $\pm$ 0.7 (4)	0.88
18 h postoperative	4.6 $\pm$ 1.4 (25)	4.4 $\pm$ 0.1 (2)	4.9 $\pm$ 1.0 (4)	0.92
PRISM III Score				
12 h postoperative	5.7 $\pm$ 3.7	4.2 $\pm$ 2.8	6.4 $\pm$ 3.4	0.30
24 h postoperative	7.6 $\pm$ 4.3	5.2 $\pm$ 2.5	7.9 $\pm$ 3.1	0.17
Days intubated	1.6 (1.1–2.8)	1.5 (0.9–2.3)	2.7 (1.3–5.7)	0.14
Days in intensive care unit	3 (2–4)	3.5 (2–4.5)	4 (2–7)	0.33
Days in hospital	7 (5–8)	7 (5.5–8)	9 (5–21)	0.08

Values are expressed as mean $\pm$ standard deviation or median (interquartile range). *P* values are determined by Fisher's exact test for diagnostic group, analysis of variance for continuous outcomes, and Kruskal-Wallis tests for hospital course variables

TGA = D-transposition of the great arteries; TOF = tetralogy of Fallot; VSD = ventricular septal defect; CPB = cardiopulmonary bypass; PRISM III = Modified Pediatric Risk of Mortality-III