Received: 12 July 2016 | Revised: 31 August 2016 | Accepted: 16 October 2016

DOI: 10.1111/chd.12426

ORIGINAL ARTICLE

WILEY Congenital Heart Disease

Cerebral tissue oxygenation index and lactate at 24 hours postoperative predict survival and neurodevelopmental outcome after neonatal cardiac surgery

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Funding information
This study was supported with the following grants: (1) CreFF Grant from Children's National Medical Center, Washington, DC [Principal Investigator: Dr. Richard A. Jonas].; (2) Saving Tiny Hearts Society Grant [Principal Investigator: Dr. Mary T. Donofrio].

Abstract

Importance: There are no well-established noninvasive biomarkers for identifying patients at risk for poor outcome after surgery for congenital heart disease. Few studies have assessed prognostic accuracy of cerebral tissue oxygenation index (cTOI) measured by near infrared spectroscopy (NIRS).

Objective: To assess the utility of noninvasive NIRS monitoring as a predictor of outcomes after neonatal cardiac surgery through measurement of cTOI. To examine the utility of noninvasive NIRS monitoring in combination with lactate concentration and inotropic score in prediction of outcomes after neonatal cardiac surgery.

Design: Prospective longitudinal cohort study.

Setting: Operating room and cardiac intensive care unit, Children's National Heart Institute.

Participants: Seventy-five patients with complex congenital heart disease undergoing surgical repair within first month of life.

Exposure: Cerebral TOI, blood lactate, and inotropic scores were measured preoperative, intraoperative and up to 24 hours postoperative.

Main Outcome Measures: Postoperative mortality and neurodevelopmental outcome assessed by the Bayley Scales of Infant Development (BSID II). Mental and motor scores were obtained at 6, 15, and 21 months. Good outcome was defined as survival and BSID mental and motor scores $\geq$70 points. Poor outcome was defined as death or BSID scores $<$70 at most recent follow-up.

Results: Cohort of 75 patients prospectively followed including 40 patients with single ventricle and 35 with two ventricles. Four patients died before discharge and ten died within 21 months. Seven patients were lost to follow-up. Among survivors with follow-up ($n = 54$), BSID was abnormal in 25 (46%). Patients with poor outcome ($n = 39$) had lower mean cTOI 60 minutes off-CPB (48% vs. 58%, $P = .003$) and 24 hours postoperative (49% vs. 59%, $P < .001$), higher lactate (8.2 vs. 5.0 mmol/L, $P = .005$) and higher inotropic scores (10 vs. 6, $P = .02$) at 24 hours postoperative. ROC analysis indicated that cTOI had moderate predictive accuracy of outcome (AUC = 0.751, $P < .001$). Multivariable regression analysis confirmed that predictive accuracy was improved using both cTOI and lactate at 24 hours postoperative (AUC = 0.813, 95% CI: 0.705–0.921, $P < .001$) with optimal cutoff values $<$58% and $>$7.4 mmol/L, respectively (sensitivity = 95%).

Conclusion: Cerebral TOI combined with lactate at 24 hours postoperative are accurate noninvasive predictive biomarkers of patient survival and neurodevelopmental outcome in neonates with CHD undergoing cardiac surgery.

KEYWORDS

congenital heart disease, lactate, near infrared spectroscopy, neurodevelopmental outcome, pediatric cardiology, tissue oxygenation

1 | INTRODUCTION

Neonates with congenital heart disease (CHD) are at risk for mortality and poor neurodevelopmental outcome (NDO).[1,2] Survival has improved with recent advances in perioperative surgical techniques and intensive care unit (ICU) management which have facilitated surgical correction of complex CHD.[2] In contrast, brain injury with subsequent developmental delay continues to be a major problem affecting up to 25% of the survivors.[3] These neurological and developmental abnormalities include diminished cognitive performance, developmental delay, language and behavioral problems, seizures, and cerebral palsy.[4–7]

Detection and early prevention of poor outcome in high risk neonates with CHD has been the focus of previous studies.[4–7] A barrier to improving NDO is the lack of real-time monitoring of brain oxygenation and risk of neurologic injury preoperatively and both in the operating room and ICU. Intraoperative and postoperative monitoring of neurological status is limited by the difficultly in monitoring hemodynamically unstable and fragile patients. The use of bedside brain ultrasound and conventional 20-lead EEG is time limited and cumbersome in the operating room and ICU, and the use of jugular bulb oximetry to measure mixed venous oxygen saturation is an invasive procedure that carries the risks of central catheter placement.[7–9]

Near-infrared spectroscopy (NIRS) has been used clinically to monitor regional cerebral oxygen saturation based on the variable absorption of different wavelengths of light by hemoglobin combined with oxygen.[10] NIRS values are mainly venous weighted as the technique measures the oxygen content on the venous side of the circulation (85% venous, 15% arterial).[10–13] NIRS can be used transcutaneously to measure the cerebral tissue oxygenation index (cTOI) providing an estimate of the cerebral oxygen supply-demand balance. It has the advantage of supplying a noninvasive, real-time, bedside measurement of cerebral oxygenation and hemodynamics which can be critical for the medical team to initiate interventions to maintain a safe cerebral oxygenation level.[10,14]

The purpose of this study is to assess the performance of noninvasive NIRS monitoring and hemodynamic variables as predictors of survival and NDO in neonates with CHD undergoing cardiac surgery.

2 | METHODS

This is a prospective longitudinal study conducted at Children's Heart Institute at Children's National Medical Center. The study has been approved by the Institutional Review Board. Parental consent was obtained. Patients included in the study were those with (a) gestational age $\geq$34 weeks, (b) postnatal age $<$1 month, and (c) diagnosed with CHD requiring open heart surgery within their first month of life. Patients were excluded from the study if they had (a) gestational age $<$34 weeks, (b) significant associated major extra-cardiac anomalies, or (c) a suspected or confirmed genetic syndrome. In addition to demographic characteristics, clinical data was collected including: (1) inotropic drugs utilized for stabilization, (2) blood gases in the preoperative, intraoperative and postoperative periods, (3) days in the ICU, (4) length of hospital stay, and (5) survival to hospital discharge and survival to outpatient assessment at 21 months.

2.1 | Near infrared spectroscopy monitoring

cTOI was measured using a near-infrared spectrometer (NIRO-200; Hamamatsu Photonics KK, Hamamatsu city, Japan).[15] The NIRS sensor was attached to the forehead, just below the hairline. The Hamamatsu monitor has the advantage of using Spatially Resolved Spectroscopy which allows calculation of cTOI rather than measurement of the usual changes of hemoglobin concentration. The tissue oxygenation index is an absolute term, independent of a tissue path length factor.[16] Calculation of the cTOI is based on the ratio of oxygenated hemoglobin to total hemoglobin and thus reflects the mean hemoglobin oxygen saturation. cTOI was obtained daily for at least 30 minutes in the preoperative period, continuously throughout surgery and continuously up to 24 hours postoperative. Data were analyzed at five time points: preoperative, post induction, on cardiopulmonary bypass (CBP), at 60 minutes off CPB and at 24 hours postoperative. Both average and minimum cTOI were analyzed at each time point to assess whether it could differentiate survivors and nonsurvivors as well as a poor NDO.

2.2 | Clinical monitoring

Blood gas and lactate concentrations were measured on CPB, 60 minutes off CPB and 24 hours postoperative. Furthermore, blood gases were obtained as frequently as clinically indicated intraoperative and postoperative. Samples were obtained from an arterial line and were processed immediately using point of care (i-STAT, Abbott Laboratories, Abbott Park, IL, USA). Lactate concentrations were analyzed at three time points: on CPB, 60 minutes off CPB and at 24 hours postoperative.

2.3 | Inotropic score

Hourly doses of all vasoactive medications were recorded for the first 24 hours postoperative. Inotropic score (IS) was calculated based on the maximum amount of inotropic support given to the patient at any time during that period. IS was calculated according to the following formula.[17]

TABLE 1 Demographics and clinical characteristics of the study population ($N = 75$)

Variable	All patients	Single ventricle patients	Two ventricle patients	*P* value
Number of patients	75	40	35	
Weight (kg)	3.5 (3.0-3.8)	3.2 (2.8-3.6)	3.5 (3.1-4.0)	.01
Patient age (days)	5 (4-8)	5 (3-7)	6 (4-8)	.03
CPB time (min)	118 (101-125)	117 (107-124)	118 (82-126)	.59
Sex				
Male	44 (59%)	23 (58%)	21(60%)	1.00
Female	31 (41%)	17 (42%)	14 (40%)	
IS	5 (5-10)	10 (5-14)	5 (3-9)	.002
ICU stay (days)	12 (6-21)	15 (12-31)	6 (4-11)	<.001
LOS (days)	24 (15-44)	30 (21-53)	16 (10-30)	<.001
Lost to follow-up	7 (9%)	2 (5%)	5 (14%)	.24
Good outcome:				
BSID ≥70	29 (39%)	8 (20%)	21 (60%)	<.001
Poor outcome:				
Death	14 (19%)	13 (32%)	1 (3%)	<.001
BSID <70	25 (33%)	17 (43%)	8 (23%)	.09

Continuous data are median and interquartile range.
Groups were compared with Mann–Whitney *U* test for continuous variables and Fisher's exact test for categorical variables. CPB, cardiopulmonary bypass; IS, inotropic score; LOS, length of stay; BSID, Bayley Scales of Infant Development.

$$\text{IS} = \text{Dopamine dose } (\mu g/kg/min) + \text{Dobutamine dose } (\mu g/kg/min) + 100 \times \text{Epinephrine dose } (\mu g/kg/min)^{16}$$

2.4 | Neurodevelopmental outcome assessment

Patients underwent neurodevelopmental assessment by a single clinical psychologist at 6, 15, and 21 months. The primary assessment tool was the Bayley Scale of Infant Development (BSID-II). BSID-II provides scores on two indexes; psychomotor Developmental Index (PDI) and Mental Developmental Index (MDI).[18] NDO was measured as mean-± standard deviation (SD) of 100 ± 15. Outcome was defined as normal in patients who survived and had BSID scores (≥70) while abnormal outcome was defined as mortality or low BSID scores (<70).[15,19,20]

2.5 | Statistical Analysis

Survivors and nonsurvivors were compared with respect to average % cTOI at preoperative, post induction, on CPB, 60 minutes off CPB, and 24 hours postoperative using repeated measures analysis of variance (ANOVA) and similarly for lactate concentration on CPB, 60 minutes off CPB and at 24 hours postoperative. Multivariable logistic regression was used to estimate the probability of mortality as well as poor outcome for average cTOI at 24 hours postoperative adjusting for diagnosis as a covariate [single ventricle (SV) or two ventricles (2V)] with significance assessed by the likelihood ratio test.[21] Receiver operating characteristic (ROC) curve analysis was applied to identify optimal cut-off values using the Youden J-index.[22] The c-statistic was utilized to evaluate the accuracy and goodness-of-fit of the predictive algorithms based on the combination of 24 hours postoperative cTOI (%) and blood lactate concentration(mmol/L) for determining the risk of mortality and poor outcome.[18] Statistical analysis was performed using IBM/SPSS Statistics (version 21.0, IBM Corporation, Armonk, NY, USA). Two-tailed values of $P < .05$ were considered statistically significant.

3 | RESULTS

We prospectively monitored a cohort of 75 neonates with CHD admitted to the CICU for surgical repair of their CHD. Median age at time of surgery was 5 days (4–8 days). Median weight at time of surgery was 3.5 kg (3.0–3.8). Patient demographics and clinical characteristics are summarized in Table 1. Out of 75 patients, 40 patients had SV physiology and 35 patients 2V. Of the 40 SV patients, 38 patients underwent a Norwood procedure. Specific cardiac pathologies are listed in Table 2. CPB was used in all patients with average duration of 118 ± 11 minutes. In CPB, dilutional ultra-filtration and PH-stat strategy were used. Goal hematocrit was 30%. Deep Hypothermic Circulatory arrest (DHCA) was used in 65 (87%) patients. Average duration of DHCA was 30 ± 21 minutes. The goal temperature during DHCA was 18°C.

Seven patients (9%) were lost to follow-up after hospital discharge and were therefore excluded from the long term NDO data. Four (5%) patients died before hospital discharge (all of them with SV), and an additional 10 (13%) patients died by 21 months of age (9 patients with

TABLE 2 Cardiac pathology of the study population ($N = 75$)

Diagnosis (procedure)	Number
Biventricular heart defects:	
D-TGA (arterial switch)	14
D-TGA + VSD (arterial switch and VSD patch)	4
DORV + hypoplastic arch (arterial switch)	1
Co A (AA reconstruction)	2
Co A + VSD (AA reconstruction + VSD patch)	3
TOF (repair)	3
TAPVR (repair)	2
Transitional AVC (repair)	2
Supra-valvular PS (supra-valvular patch)	1
VSD + ASD (patch repair)	2
Truncus arteriosus (repair)	1
Total	35
Single ventricle defects:	
HLHS (Norwood)	20
HLHS variants (Norwood)	15
DILV + TGA (Norwood)	2
Unbalanced AVC + DORV + HRV (Norwood)	1
TA + TGA + CoA (Damus–Kaye–Stansel)	2
Total	40

TGA, transposition of great arteries; VSD, ventricular septal defect; DORV, double outlet right ventricle; CoA, coarctation of the aorta; AA, aortic arch; TOF, tetralogy of Fallot; TAPVR, total anomalous pulmonary venous return; AVC, atrioventricular canal; PS, pulmonary stenosis; ASD, atrial septal defect; HLHS, hypoplastic left heart syndrome; DILV, double inlet left ventricle; HRV, hypoplastic right ventricle; TA, tricuspid atresia.

SV and one with 2V). Among the 54 survivors with follow-up information, 29 patients with BSID ≥70, of whom 11 patients had BSID between 70 and 85. Twenty-five patients had BSID scores <70 points on either MDI or PDI, or both. A total of 39 patients had poor outcome (14 deaths, 25 with low BSID scores); 30 (77%) had a SV including 13 who died by the age of 21 months and 17 with poor NDO. Out of the 35 patients with 2V, 9 (26%) patients had poor outcomes including death of one patient and 8 with poor NDO (Table 1).

3.1 | BSID neurodevelopmental scores

Patients had neurodevelopmental assessment at 6, 15, and 21 months. NDO differed in patients with SV when compared with 2V patients. At 6 months, both MDI and PDI were significantly decreased in patients with SV compared with patients with 2V. However at 15 and 21 months, only the PDI was lower in patients with SV compared with patients with 2V (Table 3).

3.2 | Cerebral TOI

Preoperative average cTOI was 55% ± 7%; preoperative minimum cTOI was 43% ± 12%. Average cTOI did not show significant difference between SV and 2V patients preoperatively, post induction and during CPB whereas average cTOI was significantly decreased in patients with SV at 60 minutes off CPB and at 24 hours postoperative (Figure 1).

Average preoperative cTOI and cTOI on CPB were not different when comparing patients who survived and those who died. Patients who survived had a higher average cTOI than those who died at 60 minutes off CPB (55% ± 10% vs. 43 ± 19%, $P < .001$) and at 24 hours postoperative (57% ± 11% vs. 42% ± 12%, $P < .001$, respectively) (Figure 2A and Table 4).

TABLE 3 Neurodevelopmental scores on both mental and motor developmental indexes at 6, 15, and 21 months

Age	All patients	Single ventricle patients	Two ventricle patients	*P* value
6 months				
Mental	87 ± 11	83 ± 13	91 ± 8	.02
Motor	76 ± 15	68 ± 15	83 ± 9	.001
15 months				
Mental	85 ± 13	82 ±16	87 ± 11	.29
Motor	76 ± 19	65 ± 20	82 ± 15	.004
21 months				
Mental	76 ± 19	72 ± 20	81 ±18	.24
Motor	74 ± 17	68 ±17	82 ± 15	.04

Minimum preoperative cTOI did not differ between patients who died and survivors. Minimum cTOI was significantly lower in patients who died compared with survivors, on CPB (34% ± 18% vs. 43% ± 14%, $P = .05$) and at 60 minutes off CPB (28% ± 20% vs. 44% ± 12%, $P < .001$). Interestingly, there was no difference in the minimum postoperative cTOI at 24 hours between patients who died and those who survived (Table 4). Patients with poor outcome had lower average cTOI within 60 minutes off CPB (49% vs. 58%, $P = .003$) and at 24 hours postoperative (49% vs. 59%, $P < .001$) (Figure 2B). There was no significant difference in the minimum cTOI between patients with poor outcomes when compared with patients with good outcomes.

3.3 | Lactate concentration

Lactate concentrations for all patients was 5.3 ± 1.8 on CPB, 6.0 ± 2.2 at 60 minutes off CPB and 6.6 ± 4.7 at 24 hours postoperative. Lactate concentration was greater in SV patients when compared with 2V

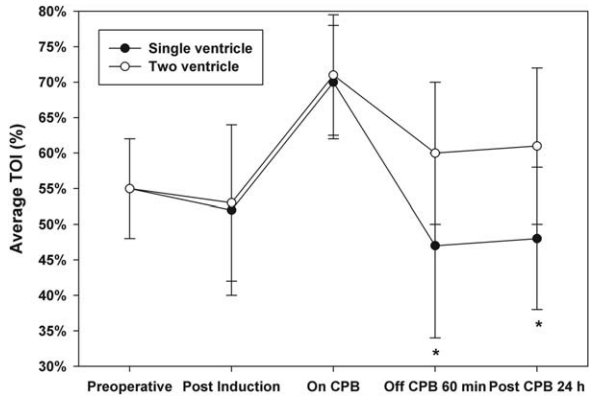

FIGURE 1 Average cTOI in patients with single ventricle and two ventricles. [Average cTOI differed significantly between the 2 groups 60 minutes off CPB and 24 hours postoperative, $P < .001$].

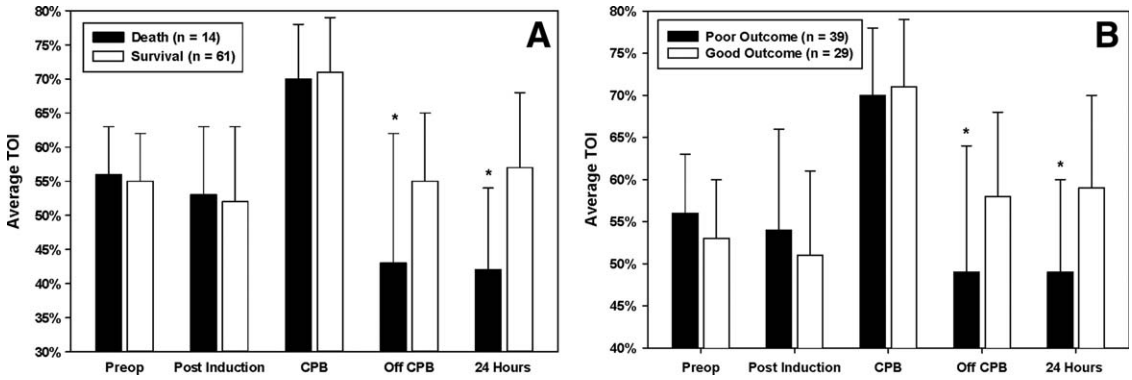

FIGURE 2 (**A**) Average cTOI in relation to mortality. [Patients who died had lower average cTOI compared with survivors at 60 minutes off CPB and at 24 hours postoperative, $P < .001$]. (**B**) Average cTOI in relation to poor outcome. [Patients with poor outcome including mortality and poor NDO had a lower average cTOI compared with survivors with good NDO at 60 minutes off CPB and at 24 hours postoperative, $P = .003$ and $P < .001$, respectively].

patients while on CPB (6.1 ± 1.5 vs. 4.4 ± 1.7, $P < .001$), 60 minutes off CPB (7.1 ± 1.7 vs. 4.7 ± 2.1, $P < .001$), and 24 hours postoperative (8.4 ±5.3 vs. 4.3 ± 2.5, $P < .001$). Patients with poor outcome had a higher lactate concentration than patients with good outcome at 60 minutes off CPB (6.5 vs. 5.4, $P = .04$) and at 24 hours postoperative (8.2 vs. 5.0, $P = .005$). On CPB, lactate concentration did not show a significant difference between patients who died and those who survived, nor between patients who had poor outcome and those who had good outcome.

3.4 | Inotropic score

Inotropic score was (8.1 ± 5.8) for all patients and was significantly higher for SV than 2V patients (10.1 ± 6.5 vs. 5.7 ± 3.7, $P < .001$). Patients who died had a higher IS at 24 hours postoperative compared with survivors (13 ± 7 vs. 7 ± 5, $P = .006$). Similarly, patients with poor outcome had higher IS compared with those with good outcome at 24 hours post-operative (10 ± 6 vs. 6 ± 5, $P = .02$).

TABLE 4 Comparison of average and minimum cTOI at time points of assessment between survivors and nonsurvivors

Variable	Mortality ($N = 14$)	Survival ($N = 61$)	P value
Average cTOI (%)			
Preoperative	56 ± 7	55 ± 7	.65
Post induction	53 ± 10	52 ± 11	.92
CPB	70 ± 8	71 ± 9	.83
Off CPB-60 min	43 ± 19	55 ± 10	<.001*
Post CPB-24 hours	42 ± 12	57 ± 11	<.001*
Minimum cTOI (%)			
Preoperative	46 ± 12	43 ± 12	.41
Post induction	43 ± 11	43 ± 13	.97
CPB	34 ± 18	43 ± 14	.05*
Off CPB-60 min	28 ± 20	44 ± 12	<.001*
Post CPB-24 hours	32 ± 12	38 ± 13	.17

Data are mean ± SD.
cTOI, cerebral tissue oxygenation index; CPB, cardiopulmonary bypass.
*Significant difference in average cTOI at 60 minutes off CPB and 24 hours postoperative while Minimum cTOI was significantly lower on CPB and at 60 minutes of CPB but not at 24 hours postoperative.

3.5 | Multivariable analysis

Multivariable logistic regression analysis evaluated 5 variables (cTOI at 60 minutes off CPB, cTOI at 24 hours postoperative, lactate at 60 minutes off CPB, lactate at 24 hours postoperative, and highest IS) and revealed that the strongest predictor of mortality and poor outcome was cTOI at 24 hours postoperative ($P < .001$). Each decrease of 1% in cTOI results in a 7% increased risk in the odds of a poor outcome (Figure 3A,B).

cTOI at 24 hours postoperative predicted outcome (AUC = 0.751). Accuracy was improved using both cTOI and lactate concentration at 24 hours postoperative (AUC = 0.804, 95% confidence interval: 0.693-0.916, $P < .001$) with cutoff values of <58% for cTOI and >7.4 mmol/L for lactate. Using the derived cutoff values for cTOI and lactate, 37 of the 39 patients with poor outcomes were correctly classified (sensitivity = 95%).

Combining cTOI and lactate concentration predicted both mortality and poor outcomes. With a cTOI <58% and lactate >7.4 mmol/L, the probability of mortality is 45%, whereas with a cTOI ≥58% and lactate ≤7.4 mmol/L, the probability of mortality is only 2%. With cTOI <58% and lactate >7.4 mmol/L, the probability of poor outcome is 90%, whereas with cTOI ≥58% and lactate ≤7.4 mmol/L, there is a 10% probability of a poor outcome (Table 5).

4 | DISCUSSION

Our study shows that NIRS monitoring to assess cTOI in combination with blood lactate concentration predicts outcomes in neonates with CHD undergoing cardiac surgery. Decreased cTOI and increased lactate concentration at 60 minutes off CPB and 24 hours postoperatively were associated with mortality and adverse NDO. cTOI <58% when combined with blood lactate >7.4 mmol/L at 24 hours postoperative achieved a sensitivity of 95% in prediction of poor outcomes.

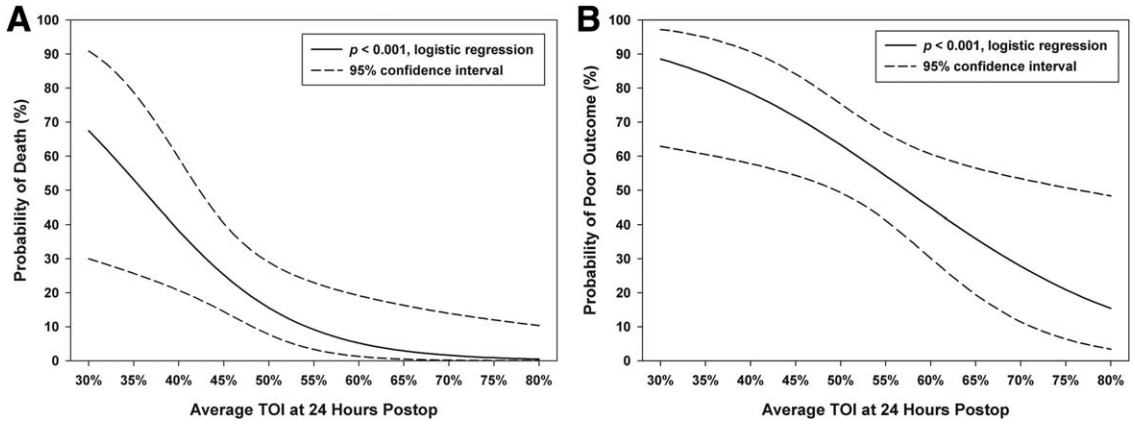

FIGURE 3 **(A)** Multivariable logistic regression curve showing mortality in relation to average cTOI; lower average cTOI is associated with the probability of death. **(B)** Multivariable logistic regression curve showing poor outcome in relation to average cTOI; each 1% decrease in average cTOI is associated with 7% increase in probability of poor outcome.

NIRS monitoring of cerebral oxygenation has been used for more than 20 years in cardiac surgery though significant debate continues about its value in physiologic monitoring to optimize brain protection and NDO.[23,24] Our study shows that cTOI measured by NIRS during the postoperative period is an accurate predictor of outcome in patients with CHD undergoing cardiac repair. Moreover, cTOI used in combination blood lactate concentration improves prediction of both mortality and poor neurodevelopmental outcome.

Average cTOI at 24 hours postoperative was the strongest predictor of outcome; each 1% decrease in the average cTOI was associated with a 7% increase in the odds of poor outcome. Of note despite this finding, the minimum cTOI at 24 hours postoperative was not predictive of outcome. These findings suggest that a cumulative low cTOI in the postoperative period is likely more critical than having a low cTOI for a brief period due to transient instability. These results highlight the concept that the "average" postoperative cTOI rather than the minimum cTOI is important, perhaps opening up the possibility of a time window for interventions that can be applied to improve overall brain oxygenation and eventually to improve outcome.

In our study, cerebral NIRS monitoring had the ability to predict adverse outcome through measurement of cTOI. This finding is in agreement with previous studies. Austin and colleagues studied multimodality neurologic monitoring using cerebral NIRS, transcranial Doppler, and EEG. Low cerebral NIRS was strongest predictor of acute neurological injury, associated with 58% of acute neurologic abnormalities.[25] Of note, most of the studies reported considered the trends and the percent changes in baseline NIRS readings rather than examining the absolute readings. In one study, a 20% reduction in cerebral oxygenation that lasted for 3 minutes was considered significant and interventions were applied regardless of the actual reading.[25] Others have challenged this approach and cautioned against using NIRS trends because waiting for a specific predefined percent decrease from the baseline may delay application of interventions to maintain cerebral oxygenation.[26] Our study supports the concept that there is likely a cutoff point for critical cerebral oxygenation that persists over time that increases the risk of poor outcomes.

The association between lower cTOI after CPB and poor outcome in our study is consistent with previous studies.[27,28] Kussman et al., found a modest relationship between lower cerebral oxygenation at 60 minutes off CPB and lower PDI after 1 year of biventricular repair.[28] Our study demonstrates the 24 hours following CPB as a critical period for cerebral injury and highlights the importance of not only intraoperative monitoring, but also continuous postoperative monitoring of cerebral oxygenation.

In our study, preoperative cTOI, both average and minimum, were not associated with poor outcome including mortality and NDO. This is in contrast to the findings of Fenton et al. who described an association between preoperative cerebral oxygen saturation <50% with mortality and preoperative cerebral oxygenation <58% with acute neurologic complications.[29] Of note is that Fenton's study utilized a single preoperative measurement of cerebral oxygenation before induction of anesthesia and they did not follow-up patients after discharge for NDO.[29] Furthermore, in our study preoperative cTOI did not differ between SV and 2V patients possibly reflecting the fact that many patients with SV, particularly those with hypoplastic left heart syndrome, tend to have pulmonary over circulation preoperatively and therefore higher cTOI.

Lactate has been used as a marker of tissue hypoxia and inadequate perfusion and has been studied as a predictor of adverse

TABLE 5 Multivariable predictive algorithm for probability of mortality and poor outcome

cTOI (%) at 24 hours	Lactate (mmol/L) at 24 hours	Probability of mortality (%)	Probability of poor outcome (%)
<58	>7.4	45 (25–65)	90 (70–97)
<58	≤7.4	15 (5–30)	65 (45–80)
≥58	>7.4	10 (1–25)	40 (15–65)
≥58	≤7.4	2 (0–12)	10 (4–30)

Predictive algorithm based on the combination of average cerebral tissue oxygenation index (cTOI) and blood lactate concentration at 24 hours postoperative. Cutoff values were determined from the Youden J-index in ROC analysis. 95% confidence intervals are shown in parentheses.

outcome after cardiac surgery.[30–32] Data supporting the use of a single lactate value to predict mortality has been controversial.[33,34] Most studies relied on a single lactate value measured in the immediate postoperative period, which might explain the discrepancy in results. Our study suggests that a high lactate concentration at 60 minutes off CPB was associated with outcome whereas lactate on CPB was not useful. In addition, the most important lactate concentration to be associated with prediction of mortality and poor outcome was at 24 hours after surgery. It is probable that survivors were able to eliminate intraoperative hyperlactatemia but those who continued to experience high lactate levels were affected by poor outcome. Moreover, this lag in rise of lactate concentration in relation to bypass might be related to the lactate being a relatively late marker of tissue under perfusion. To our knowledge, this is the first study to examine both the relationship between lactate concentration and NDO and the value of combining postoperative lactate concentration with cTOI in the prediction model for outcome following neonatal cardiac surgery. The combination of these two biomarkers greatly enhanced the sensitivity of prediction of outcomes.

4.1 | Strengths and limitations

This study was designed as a prospective single center study for NIRS validation in prediction of outcomes after neonatal cardiac surgery through measurement of cTOI. Cut off values for critical postoperative cTOI were established rather than using NIRS as a trend monitor. A limitation of the study originates from being a single center study with all operations performed by the same surgeon. Therefore, the results cannot be extrapolated to other centers. A multicenter study with a larger number of single ventricle patients is warranted to verify the generalizability of our findings and to validate how well cTOI in prediction of longitudinal NDO. A second limitation is the unavailability of arterial oxygen saturation data synchronous to cTOI data which limited the calculation of the cerebral fractional tissue oxygen extraction.

In conclusion, cTOI as measured by noninvasive NIRS and lactate concentration at 24 hours postoperative provide excellent combined accuracy in predicting survival and NDO in neonates with CHD undergoing surgical correction. Future studies are needed to assess goal directed interventions based on NIRS in making intraoperative and postoperative decisions. Prognostic algorithms and pathways for maintaining proper cerebral oxygenation and improving brain tolerance to hypoxic ischemic insults need additional investigation.

CONFLICTS OF INTEREST

None.

PRESENTATION

Abstract was initially presented in a platform presentation in the Pediatric Academic Societies (PAS) Meeting in Vancouver, Canada (May 2014).

AUTHORS' CONTRIBUTIONS

SAA: data analysis, initial drafting, critical review, and final revision.

DZ: Study design, data analysis, initial drafting, critical review, and final revision.

PG: Developmental follow-up data acquisition, and initial drafting.

KST: Data acquisition.

RAJ: Study concept/design, data analysis, initial drafting, critical review, final revision and approval of the article.

MTD: Study design, data analysis, initial drafting, critical review, final revision and approval of the article.

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How to cite this article: Aly SA, Zurakowski D, Glass P, Skurow-Todd K, Jonas RA, Donofrio MT. Cerebral tissue oxygenation index and lactate at 24 hours postoperative predict survival and neurodevelopmental outcome after neonatal cardiac surgery. *Congenital Heart Disease*. 2017;12:188–195. https://doi.org/10.1111/chd.12426