Near-Infrared Cerebral Oximetry to Predict Outcome After Pediatric Cardiac Surgery: A Prospective Observational Study

Marine Flechet, MEng; Fabian Güiza, PhD; Dirk Vlasselaers, MD, PhD; Lars Desmet, MD; Stoffel Lamote, MD; Heidi Delrue, MD; Marc Beckers, MD; Michaël P. Casaer, MD, PhD; Pieter Wouters, MSc; Greet van den Berghe, MD, PhD; Geert Meyfroidt, MD, PhD

Objectives: To assess whether near-infrared cerebral tissue oxygen saturation, measured with the FORESIGHT cerebral oximeter (CAS Medical Systems, Branford, CT) predicts PICU length of stay, duration of invasive mechanical ventilation, and mortality in critically ill children after pediatric cardiac surgery.

Design: Single-center prospective, observational study.

Setting: Twelve-bed PICU of a tertiary academic hospital.

Patients: Critically ill children and infants with congenital heart disease, younger than 12 years old, admitted to the PICU between October 2012 and November 2015. Children were monitored with the FORESIGHT cerebral oximeter from PICU admission until they were weaned off mechanical ventilation. Clinicians were blinded to cerebral tissue oxygen saturation data.

Interventions: None.

Measurements and Main Results: Primary outcome was the predictive value of the first 24 hours of postoperative cerebral tissue oxygen saturation for duration of PICU stay (median [95% CI], 4 d [3–8 d]) and duration of mechanical ventilation (median [95% CI], 111.3 hr (69.3–190.4 hr]). We calculated predictors on the first 24 hours of cerebral tissue oxygen saturation monitoring. The association of each individual cerebral tissue oxygen saturation predictor and of a combination of predictors were assessed using univariable and multivariable bootstrap analyses, adjusting for age, weight, gender, Pediatric Index of Mortality 2, Risk Adjustment in Congenital Heart Surgery 1, cyanotic heart defect, and time prior to cerebral tissue oxygen saturation monitoring. The most important risk factors associated with worst outcomes were an increased SD of a smoothed cerebral tissue oxygen saturation signal and an elevated cerebral tissue oxygen saturation desaturation score.

Conclusions: Increased SD of a smoothed cerebral tissue oxygen saturation signal and increased depth and duration of desaturation below the 50% saturation threshold were associated with longer PICU and hospital stays and with longer duration of mechanical ventilation after pediatric cardiac surgery. (*Pediatr Crit Care Med* 2018; XX:00–00)

Key Words: acute outcome; congenital heart defects; cerebral oximetry; FORESIGHT; near-infrared spectroscopy; pediatric critical care

All authors: Clinical Division and Laboratory of Intensive Care Medicine, Academic Department of Cellular and Molecular Medicine, KU Leuven, Leuven, Belgium.

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For information regarding this article, E-mail: geert.meyfroidt@uzleuven.be

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Although the outcome of children with congenital heart disease undergoing cardiac surgery has improved over the past years, significant morbidity and mortality still exist (1–4). Inadequate tissue perfusion and oxygenation are often associated with poor prognosis (5). To monitor this balance between tissue oxygen delivery and consumption, techniques such as central or mixed venous oxygen saturation, jugular or superior vena cava saturations, or arterial saturation can be used (6). Because many of these techniques require invasive blood sampling, they are not suited for continuous monitoring; hence, hemodynamic instability or critical events are possibly missed.

Near-infrared spectroscopy (NIRS) has been proposed as a technique to monitor cerebral tissue oxygen saturation ($Scto_2$) noninvasively and continuously. NIRS projects near-infrared light into the brain using disposable sensors placed on the patient's forehead. From the transmitted and reflected light, NIRS-based cerebral oximeters calculate the levels of cerebral tissue oxygen. Several studies have reported the potential of NIRS oximetry to improve patient care during cardiac surgery. In a prospective study, Murkin et al (7) randomized coronary artery bypass patients to an active $Scto_2$ display and treatment intervention protocol or to blinded $Scto_2$ monitoring. They have shown that monitoring $Scto_2$ avoids profound cerebral desaturation and is associated with a significantly lower frequency of organ dysfunction. In children undergoing surgery for congenital heart disease, low cerebral saturation measured using NIRS cerebral oximetry has been shown to be associated with worse (neurodevelopmental) outcomes (8–10).

However, the usefulness of NIRS oximetry remains unclear in pediatric postoperative care. Only a limited number of retrospective studies have investigated its association with outcomes in this setting. Spaeder et al (11) showed that a reduced postoperative $Scto_2$ variability in neonatal survivors of congenital heart disease surgery is associated with poor neurodevelopmental outcomes. In a study by Phelps et al (12), low regional cerebral oxygen saturation by NIRS in the first 48 hours after the Norwood procedure was associated with adverse outcome. Vida et al (13) reported that a postoperative $Scto_2$ desaturation score below 50% was associated with major postoperative morbidities. Whether these findings apply to patients with a cyanotic heart defect who are likely to have lower $Scto_2$ during their stay remains currently unknown. Hence, despite its increasing acceptance, high uncertainty remains in the use of NIRS oximetry for critical care decision-making (14).

We hypothesized that NIRS-based cerebral oximetry in the postoperative care of infants and children after cardiac surgery is predictive for adverse acute outcomes, such as prolonged PICU stay, prolonged duration of mechanical ventilation, and mortality. The interaction between cyanotic heart defect and $Scto_2$ was analyzed separately.

MATERIALS AND METHODS

This prospective blinded observational study was performed between October 2012 and November 2015, in the PICU of the Leuven University Hospitals, Leuven, Belgium. The Institutional Review Board approved the enrollment and clinical data collection protocol, including a waiver of parental consent for study participation. The study is registered at ClinicalTrials.gov (NCT01706497).

Study Population

Children after cardiac surgery, younger than 12 years old, with an arterial catheter in place, mechanically ventilated upon PICU admission or intubated after admission, and expected to stay at least 24 hours in the PICU, were eligible for the study. Patients were excluded if they had actual or potential brain damage, such as patients with traumatic brain injury, brain tumors, or patients after cardiopulmonary resuscitation. Patients were also excluded if they had a condition or a wound that prohibited the placement of the forehead sensors.

The following patient characteristics were prospectively collected: age, weight, gender, the Pediatric Index of Mortality (PIM) 2 score (15), cyanotic heart defect pre and post surgery (defined in **Supplemental Digital Content 1**, http://links.lww.com/PCC/A624), hemoglobin levels, arterial oxygen saturation (Sao_2) and central venous oxygen saturation (Svo_2) measured using intermittent blood sampling, and treatment with extracorporeal membrane oxygenation (ECMO). Data from surgery were retrieved from hospital records and included univentricular circulation, cardiopulmonary bypass time, aortic clamp time, and deep hypothermic circulatory therapy. Risk Adjustment in Congenital Heart Surgery (RACHS)–1 score was calculated for all patients (16). One patient had cerebral NIRS monitoring after implantation of a Levitronix CentriMag Left Ventricular Assist Device (Levitronix LLC, Waltham, MA), which we attributed a score of 6.

Cerebral NIRS Monitoring

Cerebral tissue oxygen saturation was measured continuously with NIRS, using the FORESIGHT cerebral oximeter (CAS Medical Systems, Branford, CT). All eligible patients were monitored with bilateral sensors applied to the frontotemporal area, from PICU admission until they were weaned off mechanical ventilation. Patients are generally admitted to the PICU intubation and progress quickly toward extubation in the first 2–12 hours following admission, provided that no major hemodynamic instabilities are still present. The monitor screens were blinded to the bedside clinicians with a sealed screen cover (**eFig. 1**, Supplemental Digital Content 1, http://links.lww.com/PCC/A624), and monitoring data were stored with a minute-by-minute time resolution in the Patient Data Management System (MetaVision; iMD-Soft, Needham, MA). Clinicians did not have access to the NIRS data in order not to influence the independent predictive value of the signal.

Endpoints

The primary endpoint was the predictive performance of NIRS cerebral oximetry to predict the PICU length of stay (LOS [d]). Secondary endpoints were predictive performances of NIRS cerebral oximetry to predict hospital LOS, duration of invasive mechanical ventilation (hr), hospital mortality, and mortality at 90 days after admission to the PICU. Information on vital status at 90 days was obtained from the hospital information system. To account for death as a competing risk, duration of PICU and hospital stay and duration of mechanical ventilation were penalized in nonsurvivors to maximum duration plus 1 day or plus 1 hour, respectively. Continuous outcomes were log transformed because their distributions were positively skewed which resulted in heteroscedasticity in the residuals plot. For logistic regression analysis, the outcome variables were transformed into binary outcomes using the 75th percentile as arbitrary cutoff. This way, prolonged PICU stay was defined as longer than 8 days, prolonged hospital stay as longer than 21 days, and prolonged duration of mechanical ventilation as longer than 190 hours.

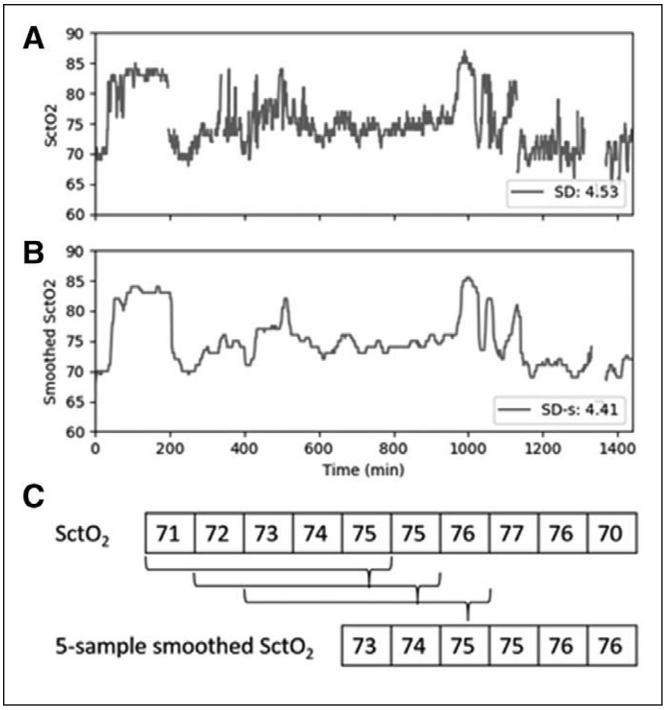

Figure 1. Example of 24-hr SD of Scto$_2$ (SD) (**A**) and SD of a smoothed Scto$_2$ signal (SD-s) (**B**), created by taking the median of a rolling 20-sample window of the initial signal. **C**, Example of the creation of a five-sample smoothed signal, created by taking the median of a rolling five-sample window of the initial signal. Scto$_2$ = cerebral tissue oxygen saturation.

Scto$_2$ Predictors

The minute-by-minute Scto$_2$ data were preprocessed as follows: first, the signal from the left and right electrodes was averaged; second, Scto$_2$ values below 20% were considered as artifacts and removed prior to analysis; third, single missing values were imputed using linear interpolation. For each patient, the following summary statistics of the preprocessed minute-by-minute Scto$_2$ were calculated and used as predictors: mean, linear trend (slope of a fitted trend line), SD of the signal (SD), and SD of a smoothed signal (SD-s) created by taking the median of a rolling 20-sample window of the initial signal (**Fig. 1**). Additionally, we calculated the variability index defined by Spaeder et al (11), using the root mean of successive squared differences (RMSSD) of minute-by-minute NIRS cerebral Scto$_2$. Finally, we calculated the desaturation score introduced by Slater et al (17) as the area under the curve for commonly investigated saturation thresholds below 50% and 60% (17–21), for patient-specific saturation thresholds below the 25 and 50th percentiles, and for saturations thresholds above 70% and 80%. We also calculated the time the saturation was below or above these thresholds. We used both percentage of area and percentage of time to account for the variation of duration in the first 24 hours of monitoring between patients.

Association Between Scto$_2$ Predictors and Outcomes

Figure 2 describes the steps undertaken to analyze the associations between the Scto$_2$ predictors and outcomes.

First, univariable linear regression was used to investigate the association of each Scto$_2$-derived predictor separately, with PICU and hospital LOS, and with duration of invasive mechanical ventilation (Fig. 2*A*). We used a bootstrap approach (5,000 bootstraps) to create CIs and evaluate the stability of each model (22). The Scto$_2$ predictors that were found to be independently and robustly associated with worse outcome were combined in a multivariable-adjusted bootstrap linear regression to assess their combined contribution for each outcome (Fig. 2*B*). In the multivariable linear regression, models were adjusted for the time interval between admission and start of NIRS monitoring and for duration of mechanical ventilation prior to the start of NIRS monitoring, respectively. Models were additionally adjusted for age, weight, gender, postoperative cyanotic versus noncyanotic heart defect, PIM2 probability of death (15), and RACHS-1 score. As patients with a cyanotic heart defect post surgery are likely to have lower Scto$_2$ during their stay and to have less favorable outcomes, interaction terms were included in the multivariable model to understand how the Scto$_2$ signal is affected by the cyanotic cardiopathy. Finally, receiver operating characteristic (ROC) curves were used to assess the ability of the individual and combined predictors to discriminate the prolonged clinical outcomes.

Second, univariable (Fig. 2*A*) and multivariable (Fig. 2*B*) logistic regression was used to

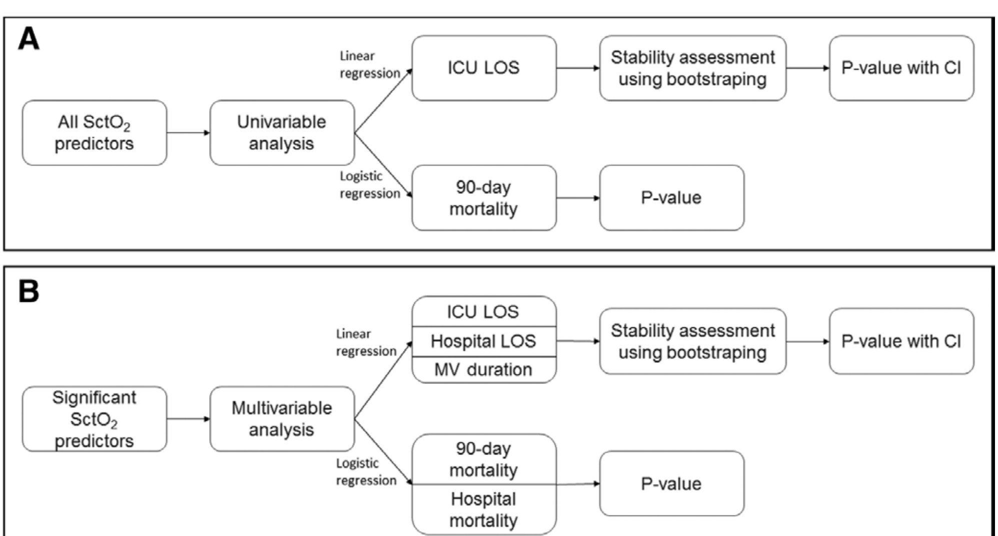

Figure 2. Scheme of analysis. **A**, Selection of significant predictors through univariable analysis. **B**, For continuous outcomes, multivariable analysis were corrected for age, gender, weight, cyanotic heart defect, Pediatric Index of Mortality (PIM) 2, Risk Adjustment in Congenital Heart Surgery 1 score, and time prior to cerebral tissue oxygen saturation (Scto$_2$) monitoring. For binary outcome, multivariable analysis were corrected for age and PIM2 score. LOS = length of stay.

investigate the association of each independent $Scto_2$-derived predictor with hospital and 90-day mortality. The low mortality prevalence precluded the use of the bootstrap approach and the adjustment for the complete list of aforementioned confounders and interaction terms. Instead, models were only adjusted for age and the PIM2 probability of death, which are strong predictors of adverse outcomes (15).

Statistical Analysis

Data are presented as means and SDs, medians and interquartile ranges (IQRs), and numbers and proportions, where appropriate. Differences between perioperative characteristics, oxygen saturation signals, and outcomes of patients with and without cyanotic heart defect were compared with analysis of variance for continuous variables and Fisher exact test for categorical variables. Statistical significance was set at *p* value of less than 0.05. All analyses were performed using Python version 2.7.13 (Python Software Foundation, http://www.python.org), Scipy version 0.18.1 (SciPy.org).

RESULTS

Study Population

One hundred seventy-seven patients were included in the study. Demographics data, perioperative risk factors, and outcomes are presented in **Table 1**. Median (IQR) age at PICU admission was 4 months (1–14 mo). Median (IQR) weight upon PICU admission was 5.2 kg (3.8–8.0 kg). Overall, 107 (60.5%) were male, 45 (25.4%) had a univentricular physiology, 11 (6.2%) underwent deep hypothermic circulatory arrest, 114 (64.4%) had a cyanotic heart defect pre surgery, 70 (39.5%) had a cyanotic heart defect post surgery, and eight (4.5%) were treated with ECMO during their stay. Median cardiopulmonary bypass duration was 84.5 minutes (56.3–113.8 min). Median aortic clamp time was 54.5 minutes (33.0–76.8 min). Median (IQR) PICU and hospital LOS were 4 days (3–8 d) and 10 days (6–21 d), respectively. Median (IQR) duration of mechanical ventilation was 111.3 hours (69.3–190.4 hr). Hospital and 90-day mortality were 5.1%. Median (IQR) duration of NIRS monitoring during the first 24 hours was 21.4 hours (9.3–24 hr), with a median (IQR) delay between PICU admission and start of NIRS monitoring of 1.1 hours (0.5–3.8 hr). The median (IQR) delay between start of mechanical ventilation and start of NIRS monitoring was 0.5 hour (0.1–2.1 hr).

During the first 24 hours of monitoring, mean (SD) hemoglobin was 11.4 (1.6) g/dL. Mean (SD) Sao_2, Svo_2, and $Scto_2$ were 93% (9%), 58% (18%), and 70% (8%), respectively. Patients with a postoperative cyanotic heart defect had more often a univentricular physiology ($p < 0.0001$), significantly higher RACHS-1 score ($p = 0.0002$), higher hemoglobin levels ($p = 0.0001$), lower Sao_2 ($p < 0.0001$), lower $Scto_2$ ($p < 0.0001$), longer PICU ($p = 0.002$) and hospital stays ($p < 0.0001$), longer duration of mechanical ventilation ($p = 0.002$), and higher hospital mortality ($p = 0.03$) compared to patients with acyanotic heart lesions (Table 1).

Association Between $Scto_2$ Predictors and PICU LOS, Hospital LOS and Duration of Mechanical Ventilation

Univariately, the $Scto_2$ mean ($p = 0.0003$), the SD ($p < 0.0001$), the SD-s ($p < 0.0001$), the RMSSD ($p = 0.03$), the percentage of time below 50% ($p < 0.0001$) and 60% ($p < 0.0001$), above 70% ($p = 0.02$), and below the patient's median ($p = 0.002$), and the desaturation score below 50% ($p < 0.0001$), 60% ($p < 0.0001$), and above 70% ($p = 0.03$) were associated with PICU LOS (**eTable 1**, Supplemental Digital Content 1, http://links.lww.com/PCC/A624). To reduce collinearity in the multivariable analysis, the significant predictors least associated with LOS (SD, desaturation score, and percentage of time below 60%, above 70%, and below the patient's median) were removed from further analysis.

Both the SD-s and the desaturation score below 50% remained associated with adverse clinical outcomes when considered individually (**eTable 2**, Supplemental Digital Content 1, http://links.lww.com/PCC/A624) and combined (**Table 2**) in a multivariable analysis corrected for age, weight, gender, PIM2, RACHS-1 score, postsurgery cyanotic heart defect, and time prior to NIRS monitoring. The interaction analysis (**Table3**) revealed that cyanotic cardiopathy influences the association between $Scto_2$ predictors and outcomes. In patients with acyanotic heart defect, both the desaturation score and the SD-s contribute to the adverse outcome, whereas in patients with a cyanotic heart defect, it is mainly the SD-s that contributes to the adverse outcome.

In a ROC curve analysis, the SD-s was more discriminant than the desaturation score below 50% (**eFigs. 2** and **3**, Supplemental Digital Content 1, http://links.lww.com/PCC/A624). Finally, the model combining the SD-s, the desaturation score below 50%, and corrected for confounders had excellent discrimination for all clinical outcomes (**Fig. 3**) (AUC [95% CI], 0.94 [0.94–0.94] for prolonged PICU stay; AUC 0.93 [0.93–0.93] for prolonged hospital stay; AUC 0.94 [0.94–0.94] for prolonged duration of mechanical ventilation).

Association Between $Scto_2$ Predictors and Hospital and 90-Day Mortality

Univariately (**eTable 3**, Supplemental Digital Content 1, http://links.lww.com/PCC/A624), and after correction for age and the PIM2 score (**eTable 4, *A*** and ***B***, Supplemental Digital Content 1, http://links.lww.com/PCC/A624), none of the investigated $Scto_2$ predictors were associated with increased risk of mortality (hospital or 90-d).

DISCUSSION

In this study, $Scto_2$ was monitored prospectively in the early postoperative period of a large pediatric cohort after cardiac surgery. We investigated the association between outcome and NIRS cerebral oximetry predictors identified in previous studies and several new metrics calculated from the NIRS time course. We found that an increased depth and duration of desaturation below the 50% saturation threshold and an increased SD-s in the first 24 hours after cardiac surgery are associated with longer PICU and hospital stays and with longer

TABLE 1. Baseline Characteristics and Outcomes

Characteristics	All	Cyanotic Heart Defect	Acyanotic Heart Defect	*p*
n	177	70	107	NA
Demographics				
Age, mo, median (IQR)	4 (1–14)	4.5 (1–11)	4 (1.5–17)	0.15
Weight, kg, median (IQR)	5.2 (3.8–8.0)	5.3 (3.6–7.9)	5.2 (3.8–9.3)	0.13
Male gender, *n* (%)	107 (60.5)	42 (60.0)	65 (60.7)	0.92
Pediatric Index of Mortality 2 probability of death, median (IQR)	0.11 (0.04–0.24)	0.21 (0.11–0.35)	0.05 (0.03–0.15)	< 0.0001
Intraoperative				
Cyanotic heart defect before surgery, *n* (%)	114 (64.4)	70 (100.0)	44 (41.1)	< 0.0001
Risk Adjustment in Congenital Heart Surgery-1 score, *n* (%)				0.0002
1	11 (6.2)	0 (0.0)	11 (10.3)	
2	73 (41.2)	26 (37.1)	47 (43.9)	
3	59 (33.3)	25 (35.7)	34 (31.8)	
4	20 (11.3)	8 (11.4)	12 (11.2)	
5	1 (0.6)	0 (0.0)	1 (1.0)	
6	13 (7.3)	11 (15.7)	2 (1.8)	
Univentricular physiology, *n* (%)	45 (25.4)	36 (51.4)	9 (8.4)	< 0.0001
Cardiopulmonary bypass time, min, median (IQR)[b]	84.5 (56.3–113.8)	90 (58–132.5)	77 (55–110)	0.14
Aortic clamp duration, min, median (IQR)[b]	54.5 (33–76.8)	58 (0–74)	53 (37.5–77)	0.09
Deep hypothermic circulatory arrest, *n* (%)[c]	11 (6.2)	6 (8.6)	5 (4.7)	0.34
Postoperative				
Cyanotic heart defect post surgery, *n* (%)	70 (39.5)	70 (100.0)	0 (0.0)	NA
Extracorporeal membrane oxygenation during PICU stay, *n* (%)	8 (4.5)	6 (8.6)	2 (1.9)	0.06
Hemoglobin[d], g/dL, mean (IQR)	11.4 (1.6)	11.9 (1.7)	10.9 (1.5)	0.0001
Arterial oxygen saturation[d], %, mean (SD)	93.09 (9.0)	85.3 (9.8)	98.0 (2.8)	< 0.0001
Svo_2[d], %, mean (SD)[a]	58.4 (18.4)	54.0 (19.9)	63.9 (14.5)	0.28
$Scto_2$[d], %, mean (SD)	70.2 (8.0)	66.1 (8.4)	73.0 (6.4)	< 0.0001
Duration of $Scto_2$ monitoring[d], hr, median (IQR)	19.5 (6.7–23.4)	21.8 (12.3–23.6)	16.6 (7.0–23.0)	0.03
Outcomes				
PICU LOS, d, median (IQR)	4.0 (3.0–8.0)	6.0 (4.0–14.0)	4.0 (2.0–6.5)	0.002
Hospital LOS, d, median (IQR)	10.0 (6.0–21.0)	16.0 (8.0–30.5)	8.0 (6.0–13.0)	< 0.0001
Duration of invasive mechanical ventilation, hr, median (IQR)	111.3 (69.3–190.4)	143.0 (92.2–338.8)	93.9 (49.9–153.6)	0.002
Mortality 90-d, *n* (%)	9 (5.1)	6 (8.6)	3 (2.8)	0.16
Hospital mortality, *n* (%)	9 (5.1)	7 (10.0)	2 (1.9)	0.03

IQR = interquartile range, LOS = length of stay, NA = not applicable, $Scto_2$ = cerebral tissue oxygen saturation, Svo_2 = venous oxygen saturation.
[a]Measured in 18 patients.
[b]Available in 142 patients.
[c]Available in 140 patients.
[d]Measured during first 24 hr.
p value is shown for comparison between patients with postoperative cyanotic versus acyanotic heart defect.

TABLE 2. Multivariable Association Between Cerebral Tissue Oxygen Saturation and Continuous Outcomes for All Patients

	Outcomes	All Patients (n = 177) – Continuous Outcomes		
		Coefficient	R-squared	p
$Scto_2$ predictors	PICU LOS			
SD-s		0.12 (0.12–0.12)	0.609 (0.608–0.611)	0.009 (0.008–0.010)
Desaturation score below 50%		0.43 (0.42–0.44)	0.609 (0.608–0.611)	0.003 (0.002–0.004)
$Scto_2$ predictors	Hospital LOS			
SD-s		0.10 (0.10–0.10)	0.599 (0.597–0.600)	0.006 (0.005–0.007)
Desaturation score below 50%		0.30 (0.29–0.30)	0.599 (0.597–0.600)	0.01 (0.01–0.01)
$Scto_2$ predictors	Duration of mechanical ventilation			
SD-s		0.12 (0.11–0.12)	0.594 (0.592–0.595)	0.01 (0.01–0.02)
Desaturation score below 50%		0.41 (0.40–0.41)	0.594 (0.592–0.595)	0.006 (0.005–0.008)

LOS = length of stay, $Scto_2$ = cerebral tissue oxygen saturation, SD-s = SD of the smoothed signal.
Association between $Scto_2$ and LOS or duration of mechanical ventilation was corrected for age, weight, gender, Pediatric Index of Mortality 2, Risk Adjustment in Congenital Heart Surgery 1, and cyanotic heart defect and time prior to near-infrared spectroscopy monitoring.

duration of mechanical ventilation, even after correction for several confounders.

Our findings support previous studies reporting that the $Scto_2$ desaturation score or low NIRS cerebral saturation is a predictor of adverse outcomes. Slater et al (17) introduced this desaturation score and showed that intraoperatively, an elevated desaturation score below 50% was associated with longer hospital stay. Fischer et al (8) reported that an increased intraoperative desaturation score below 60% was associated with adverse outcome during aortic arch surgery. Vida et al (13) reported that the postoperative desaturation score below 50% was associated with major postoperative morbidities. In another study investigating postoperative NIRS after the Norwood procedure, Phelps et al (12) found that mean $Scto_2$ below 56% was a risk factor for subsequent adverse outcomes. Finally, Hansen et al (23) reported that the postoperative mean $Scto_2$ of patients with hypoplastic left heart syndrome was lower in patients with cardiac complications within 48 hours.

Expanding on these studies, we investigated alternative analytic approaches of the NIRS cerebral oxygen saturation time course. We found that an increased SD-s, which is a measure of variability of the low frequency components of the $Scto_2$ signal, was univariately associated with worse outcomes. Interestingly, this measure of variability remained an independent predictor in addition to the desaturation score and was a stronger predictor of poor outcome in patients with cyanotic heart lesions. Combining both resulted in excellent discrimination for prolonged stay and prolonged mechanical ventilation. The physiologic explanation for the association between an increased SD and worse clinical outcomes is unclear and should be investigated further. It has been hypothesized that NIRS oximetry could be used to assess cerebrovascular autoregulation (11, 24). In a recent study, Spaeder et al (11) introduced the cerebral tissue oxygenation index variability, which is a measure of variability of the high-frequency components of the $Scto_2$ signal (25), as the RMSSD of averaged 1-minute cerebral tissue oxygenation index values for both the intraoperative and first 24 hours postoperative phases of monitoring. They found that a reduced cerebral tissue oxygenation index variability is associated with poor neurodevelopmental outcomes in neonates after congenital heart surgery and suggest that this reduced measure of variability might be a surrogate for impaired cerebral autoregulation. In our study, which included children on average older than the neonatal age and in which we have used a different cerebral oximeter, a reduced RMSSD was not significantly associated with longer PICU or hospital stays, nor with longer duration of mechanical ventilation, after adjustment for confounders. Subsequent studies are necessary to confirm that the $Scto_2$ variability could be used as a surrogate of impaired autoregulation.

Evidently, patients with postsurgery cyanotic heart lesions had a lower mean Sao_2 and increased hemoglobin levels. Our study revealed significant differences in $Scto_2$ between patients with cyanotic versus acyanotic heart defect, a finding also reported in the pilot study by Tume and Arnold (26). Notwithstanding this statistical difference, in spite of their lower Sao_2, patients with cyanotic heart lesions are still able to preserve brain tissue oxygenation as measured by NIRS, within what would be considered a clinically acceptable range. In these patients, the SD-s was a better predictor of adverse outcomes than the desaturation score. To our knowledge, this is the first large study investigating the interaction of cyanotic cardiopathy and $Scto_2$. Our findings suggest that the pediatric population with cyanotic heart defect could benefit from different reference values of NIRS cerebral oxygen saturation.

The early recognition of children at risk after surgery for congenital heart defects could trigger interventions with the potential to improve outcome and avoid morbidity. In this study, we have discovered two novel metrics, the SD-s as a measure of $Scto_2$ variability and the desaturation score below

TABLE 3. Association Between Cerebral Tissue Oxygen Saturation and Continuous Outcomes Including Interactions Terms

	Outcomes	Coefficient	R-squared	*p*
$Scto_2$ predictors	PICU LOS			
Cyanotic		−0.43 (−0.44 to −0.42)	0.640 (0.639–0.642)	0.04 (0.04–0.05)
SD-s * cyanotic		0.21 (0.21–0.21)	0.640 (0.639–0.642)	0.0003 (0.0003–0.0004)
Desaturation score below 50% * cyanotic		−0.84 (−0.85 to −0.83)	0.640 (0.639–0.642)	0.004 (0.004–0.005)
Desaturation score below 50% * SD-s		0.18 (0.18–0.18)	0.640 (0.639–0.642)	< 0.0001 (< 0.0001–< 0.0001)
$Scto_2$ predictors	Hospital LOS			
Cyanotic		−0.18 (−0.19 to −0.17)	0.624 (0.623–0.626)	0.26 (0.25–0.27)
SD-s * cyanotic		0.16 (0.16–0.16)	0.624 (0.623–0.626)	0.0008 (0.0006–0.0009)
Desaturation score below 50% * cyanotic		−0.66 (−0.67 to −0.66)	0.624 (0.623–0.626)	0.006 (0.005–0.007)
Desaturation score below 50% * SD-s		0.13 (0.13–0.14)	0.624 (0.623–0.626)	0.0002 (0.0002–0.0003)
$Scto_2$ predictors	Duration of mechanical ventilation			
Cyanotic		−0.44 (−0.45 to −0.43)	0.626 (0.625–0.627)	0.04 (0.04–0.05)
SD-s * cyanotic		0.21 (0.21–0.21)	0.626 (0.625–0.627)	0.0004 (0.0004–0.0005)
Desaturation score below 50% * cyanotic		−0.86 (−0.87 to −0.85)	0.626 (0.625–0.627)	0.004 (0.004–0.005)
Desaturation score below 50% * SD-s		0.18 (0.18–0.18)	0.626 (0.625–0.627)	0.0001 (0.0001–0.0002)

LOS = length of stay, $Scto_2$ = cerebral tissue oxygen saturation, SD-s = SD of the smoothed signal.

Association between $Scto_2$ and LOS or duration of mechanical ventilation was corrected for age, weight, gender, Pediatric Index of Mortality 2, Risk Adjustment in Congenital Heart Surgery 1 and time prior to monitoring.

50%, which have a robust association with outcome. Whether they provide additional and clinically relevant information in addition to conventional cardiovascular monitoring at the patient's bedside could not be assessed in this observational trial but remains an interesting hypothesis that requires further investigation. The physiologic meaning behind the association between an increased $Scto_2$ variability (SD-s) and worse outcome, and whether it represents impaired cerebrovascular autoregulation, should be examined as well. The desaturation score below 50% might give the clinician an idea on the cumulative burden of low cerebral perfusion in a particular child and might be used as an early trigger to perform additional clinical, radiologic, or electrophysiologic tests to detect neurocognitive dysfunction. Pragmatic clinical trials can be set up to examine whether providing this new information to clinicians improves the outcome. For instance, the benefit of additional heart rate variability (HRV) monitoring in neonates was examined in a randomized clinical trial, where it could be demonstrated that displaying the HRV monitor was able to improve the outcomes of these infants, as compared to when the monitor was blinded (27). In addition, the cost-effective potential of NIRS-based hemodynamic management after surgery for congenital heart defects should be addressed in future studies.

As the survival in children with congenital heart disease has improved, the focus has shifted to morbidity. The early recognition of patients at risk for poor outcome could trigger interventions to improve outcome because it allows the PICU staff to take early measures to stabilize the patient. As such, continuous display of the two metrics described in this study, the SD-s as a measure of $Scto_2$ variability and the desaturation score below 50%, could provide extra information to the clinician in addition to conventional cardiovascular monitoring. However, the two metrics are currently not displayed by available cerebral oximeters, and it remains unclear how caregivers could improve or modify $Scto_2$ variability. It remains unproven whether these prognostic markers can be used as therapeutic targets. Pragmatic clinical trials can be set up to examine whether adding a new monitor or variable, and providing information to clinicians, improves the outcome. For instance, HRV monitoring has been shown to trigger earlier interventions for sepsis and improve the outcomes in neonates. $Scto_2$ variability (SD-s) robustly associates with worse outcome,

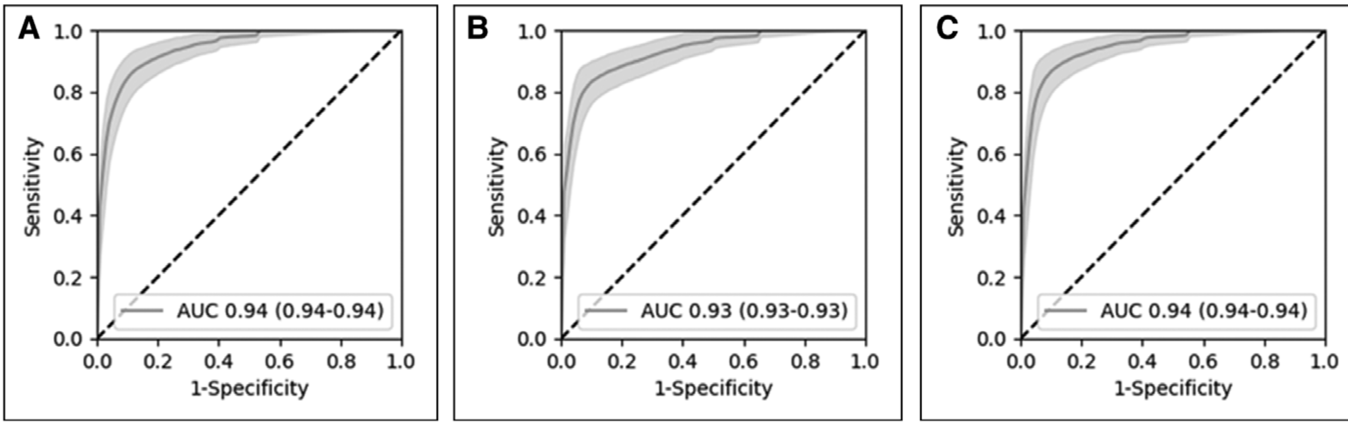

Figure 3. Receiver operating characteristic (ROC) curve and 95% CI of the bootstrap model combining the SD of the smoothed cerebral tissue oxygen saturation signal, the desaturation score below 50% and corrected for confounders. **A**, Prolonged PICU length of stay (LOS) (LOS > 8 d): area under the ROC curve (AUC) (95% CI), 0.94 (0.94–0.94); **B**, prolonged hospital LOS (LOS > 21 d): AUC, 0.93 (0.93–0.93); **C**, prolonged duration of mechanical ventilation (duration > 190 hr): AUC, 0.94 (0.94–0.94).

and we believe that the physiologic meaning behind this variable should be examined as well, and whether, for instance, it represents impaired cerebrovascular autoregulation. From a conceptual point of view, we hypothesize that the desaturation score below 50% might give the clinician an idea on the cumulative burden of low cerebral perfusion in a particular child and might be used as a trigger for clinical, radiologic, or electrophysiologic signs of neurocognitive dysfunction. In addition, the cost-effective potential of NIRS-based hemodynamic management after surgery for congenital heart defects is not known.

This study has several limitations. First, due to its single-center design, the findings highlighted in this study might not be generalizable to other populations and therefore should be validated in adequately powered prospective studies. Second, the typical low mortality prevalence of the pediatric cohort precluded any robust bootstrap analysis and might have underpowered our results related to hospital and 90-day mortality. This might explain why our results did not show that $Scto_2$ provides additional prognostic value for mortality. Third, as the baseline $Scto_2$ (28) was not registered prior to surgery, we could not assess trend changes compared with the patients' baselines. Nevertheless, this increases the applicability of our findings, as several centers might not register this cerebral oximeter baseline. Fourth, the calculation of the $Scto_2$ SD might be affected by the duration of cerebral oximetry monitoring which was shorter in patients with acyanotic heart defect. Finally, the observational design of the study prevents any conclusion on the clinical benefit of using $Scto_2$ for postoperative management.

This study has several strengths. First, it is prospective in design and hence detailed in data collection. Second, it included a large patient population that enabled to perform robust statistical analysis with correction for confounders, most noticeably for cyanotic heart defect (except for the mortality analysis) and for PIM2. The analysis was based on bootstrapping, which also increased the robustness and generalizability of the findings. Third, because the clinicians were blinded to $Scto_2$ data, treatment bias was excluded. Finally, this study is the first of its kind to study the interaction between NIRS cerebral oximetry and cyanotic heart defect in a critical care setting.

CONCLUSIONS

Increased desaturation below 50% and increased $Scto_2$ variability in the early postoperative period after cardiac surgery were found to be associated with longer PICU and hospital stays and with longer duration of mechanical ventilation, even after correction for several confounders. Furthermore, our study highlighted the difference in cerebral oxygen saturation between patients with cyanotic versus acyanotic heart defect. Hence, we recommend that future studies should be adequately powered to analyze these populations separately.

As this study was observational, our findings cannot support any conclusions regarding postoperative management of critically ill children after cardiac surgery. Opportunities for using the desaturation score and the variability of $Scto_2$ to drive therapeutic interventions remain to be investigated.

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