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CHAPTER 4

CEREBRAL OXYGENATION DURING PEDIATRIC CONGENITAL CARDIAC SURGERY AND ITS ASSOCIATION WITH OUTCOME: A RETROSPECTIVE OBSERVATIONAL STUDY

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Chapter 4

Cerebral oxygenation during pediatric congenital cardiac surgery and its association with outcome: a retrospective observational study
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Abstract

Purpose: Non-invasive cerebral oxygen saturation ($RcSO_2$) monitoring is an established tool in the intraoperative phase of pediatric congenital cardiac surgery (CCS). This study investigated the association between $RcSO_2$ and postoperative outcome by investigating both baseline $RcSO_2$ values and intraoperative desaturations from baseline.

Methods: All CCS procedures performed in the period 2010-2017 in our institution in which $RcSO_2$ was monitored were included in this historical cohort study. Baseline $RcSO_2$ was determined after tracheal intubation, before surgical incision. Subgroups were based on cardiac pathology and degree of intracardiac shunting. Poor outcome was defined based on length of stay (LOS) in the intensive care unit (ICU)/hospital, duration of mechanical ventilation (MV), and 30-day mortality. Intraoperatively, $RcSO_2$ total time below baseline (TBBL) and $RcSO_2$ time-weighted average (TWA) were calculated.

Results: Data from 565 patients were analyzed. Baseline $RcSO_2$ was significantly associated with LOS in ICU (odds ratio (OR) per percentage decrease in baseline $RcSO_2$, 0.95; 95% confidence interval (CI), 0.93 - 0.97; P<0.001), with LOS in hospital (OR: 0.93; 95% CI 0.91 - 0.96; P<0.001), with MV duration (OR: 0.92; 95% CI: 0.90 - 0.95; P<0.001) and with 30-day mortality (OR: 0.94; 95% CI: 0.91 - 0.98; P = 0.007). $RcSO_2$ TWA had no associations, while $RcSO_2$ TBBL had only a small association with LOS in ICU (OR: 1.02; 95% CI: 1.01 - 1.03; P<0.001), MV duration (OR: 1.02; 95% CI: 1.01 - 1.03; P = 0.002), and LOS in hospital (OR: 1.02; 95% CI: 1.01 - 1.04; P<0.001).

Conclusion: In pediatric patients undergoing cardiac surgery, low baseline $RcSO_2$ values measured after tracheal intubation were associated with several adverse postoperative outcomes. In contrast, the severity of actual intraoperative cerebral desaturation was not associated with postoperative outcomes. Baseline $RcSO_2$ measured after tracheal intubation may help identify patients at increased perioperative risk.

Introduction

The survival of pediatric patients with congenital heart disease (CHD) that undergo congenital cardiac surgery (CCS) has improved substantially in the last decades.[1] Still, in the (early) postoperative phase following CCS, mortality remains increased.[1,2] Especially in the perioperative phase, CCS procedures can be complicated by organ injury[3] such as acute kidney injury[4], and adverse neurologic events such as seizures and strokes.[5] The development of such complications can prolong treatment in the intensive care unit (ICU), including protracted duration of mechanical ventilation (MV), and can lead to longer hospitalization, which is associated with increased morbidity and mortality[1–3,6], along with higher costs.[1,6,7]

The use of cerebral near-infrared spectroscopy (NIRS) for measuring cerebral oxygen saturation ($RcSO_2$) has gained an established role in the perioperative monitoring of cerebral perfusion and oxygenation in pediatric CCS procedures.[8,9] Yet, its effect on influencing outcome by improving perioperative hemodynamic management in CCS remains elusive; in particular conditions of CCS, e.g., in surgical correction of the hypoplastic left heart syndrome[10], $RcSO_2$ was shown to predict postoperative outcome and improve postoperative outcome only in small studies.[11]

The spectrum of CHD is, however, broad with substantial differences in cardiopulmonary anatomy and pathology—associated differences in perioperative NIRS readings precludes generalization of perioperative $RcSO_2$ readings.[12–14]

Moreover, the influence of intraoperative cerebral desaturation on postoperative outcome in this patient population is unclear. There is also no evidence that prevention of intraoperative cerebral desaturation will reduce the likelihood of an adverse (neurologic) event.

Therefore, the primary goal of this study was to investigate whether there is an association between postoperative outcome and $RcSO_2$ values determined either at baseline (after induction of general anesthesia and tracheal intubation, pre-incision) or during the intraoperative phase in a broad population of pediatric CHD patients undergoing CCS.

Methods

Design and selection criteria

This was a historical cohort study of pediatric patients undergoing CCS in our institution from January 2010 until December 2017. The study has been approved by the local ethics committee (University Medical Center Groningen, Netherlands, Registration number: 2016/036; 22 February 2016) and the requirement for written informed consent was waived by the institutional review board given its retrospective design. This manuscript adheres to the applicable Strengthening the Reporting of Observational Studies in Epidemiology guideline.

All elective cases of pediatric CCS were included for analysis when a) the surgical procedure involved surgical correction of a congenital cardiac problem, and b) $RcSO_2$ was monitored continuously in the intraoperative period.

To account for differences in congenital cardiac conditions, patients were divided into four subgroups as described previously[14]: ''no cyanosis, no shunting'', ''no cyanosis, but left-to-right (L–R) shunting'', ''cyanosis without L–R shunting'' and ''cyanosis with L–R shunting''.

Anesthetic management

Given the historical character of the current study, induction and maintenance of anesthesia, and intraoperative hemodynamic management in response to $RcSO_2$ reductions were at the discretion of the attending anesthesiologist. General anesthesia was induced either by inhalation using sevoflurane or intravenously using propofol or etomidate. Maintenance of anesthesia was achieved with continuous infusion of propofol or midazolam and sufentanil. Muscle relaxation was achieved using rocuronium or pancuronium. Ventilation was adjusted to the patient's individual weight, physiology, and desired intrathoracic pressure using either pressure- or volume-controlled mode. Arterial oxygen saturation, five-leads continuous electrocardiogram, and end-tidal carbon dioxide ($etCO_2$) were monitored continuously through the operation. Invasive blood pressure was also monitored through cannulation of the radial or femoral artery. The central vein was accessed through the internal jugular, subclavian, or femoral vein, depending on patient and surgical characteristics. Arterial and venous blood gas samples were taken during the operation at appropriate time points. Cerebral oxygen saturation was measured by NIRS (INVOS® 5100C cerebral oximetry monitor; Medtronic, MN, USA). One or two pediatric sensors were placed on either side of the forehead, depending on the preference of the attending anesthesiologist, and the size of the child. In the study period, there was no hemodynamic optimization algorithm on which interventions were based. Also, transesophageal echocardiography, continuous cardiac output monitoring, and somatic oxygen saturation monitoring were not used routinely and were not further considered in this retrospective study. Anesthesiologists were not blinded to the $RcSO_2$ measurements.

Data collection and handling

In our institution, all cardiothoracic surgery operating rooms are equipped with medical grade computers for collecting the electronic medical records, including the continuous registration of data from the ventilator and vital signs monitor (IntelliVue MX800, Philips, Eindhoven, The Netherlands). For the purpose of this study, relevant data were extracted to a separate database (Excel, Microsoft, Redmond, USA) for further analysis.

Along with all intraoperative data, patient characteristics were collected (diagnosis, sex, age, weight, and height at the time of surgical intervention). Also, the duration of surgery, cardiopulmonary bypass (CPB) time, and aorta clamping time were collected.

An automated algorithm was used to eliminate $RcSO_2$ artefacts: $RcSO_2$ values were omitted when 1) values were implausible, i.e., below 15% and above 95% (according to the manufacturer specifications)[15], and 2) obvious artefacts were observed, which were defined as abrupt changes in three consecutive values by more than 50% and an abrupt return to at least 80% of the first value. Additionally, all data were reviewed manually by two researchers independently to account for obvious artefacts not covered by the algorithm. When a mutual decision on artefactual data could not be reached, the case was excluded. Per patient, baseline $RcSO_2$ was defined at two minutes before surgical incision, as $RcSO_2$ was assumed to have reached steady-state conditions with an inspired fraction of oxygen (FiO_2) between 0.3 and 0.4, and $etCO_2$ between 5 and 6% at that time point. Data were reviewed visually to assure that baseline $RcSO_2$ was defined at an appropriate, hemodynamically stable time point.
In case of two simultaneous $RcSO_2$ values (bi-frontal measurement), the mean of both values was taken and established as the baseline value per patient.
Additionally, the Society of Thoracic Surgeons- European Association for Cardio-Thoracic Surgery (STS- EACTS) mortality score, which primarily depends on the complexity of the surgical intervention, was calculated per patient.[16,17]

Outcomes
The distribution of outcome variables was calculated per subgroup (as based on the congenital cardiac pathology described above) to provide an assessment of ''poor outcome'' per subgroup, since it was assumed that the absolute values of the outcome variables would substantially differ per subgroup. Here, ''poor outcome''—which indicates a protracted postoperative duration of MV or LOS on the ICU or in the hospital— was defined by dichotomization, for which values above the third quartile were considered a ''poor outcome''. Secondary, in-hospital mortality, 30-day mortality, and one-year mortality after surgery were investigated. All outcome variables were defined before the start of data collection.

Statistical analysis
Per patient, the individual $RcSO_2$ baseline values (defined as outlined above) served as basis for subsequent statistical analyses. Intraoperative declines in $RcSO_2$ relative to this baseline were calculated as the individual time below $RcSO_2$ baseline (TBBL). After calculating the individual area under the curve (AUC = product of absolute $RcSO_2$ deviation below baseline and the corresponding duration in minutes), the time-weighted average (TWA) of intraoperative desaturations could be calculated, which is equivalent to dividing the AUC by the individual duration of surgery.[18]
The relationship between outcome and $RcSO_2$ was assessed using a logistic regression model, which included the variables baseline $RcSO_2$, TBBL, TWA, and the congenital cardiac subgroup (the latter accounted for the different diagnoses). These predictors were entered in a stepwise backward model using the likelihood ratio statistic for each of the three outcome variables LOS in ICU, LOS in hospital, and length of MV. For the relationship with 30-day mortality, the STS-EACTS score was added to the model.

Goodness of fit was assessed using the Hosmer-Lemeshow test and associated odds ratios (OR) are given to assess the odds after a unit change in the investigated predictors. Receiver operating characteristics (ROC) analysis was performed to assess the predictive ability of baseline $RcSO_2$ with regard to mortality in terms of sensitivity and specificity. Optimal cut-off values were calculated using the Youden index. The STS-EACTS score was included in this analysis as a reference. The ROC-derived optimal baseline $RcSO_2$ cut-off value was included in a Kaplan- Meier survival analysis for comparison of mortality.

For all performed tests, statistical significance was set at a P value of < 0.05. Tests were adjusted for multiple testing to control for the family-wise inflation of type I error rate, when deemed relevant. All tests were performed two-sided. All data were collected and synchronized in Microsoft Excel 2010 (Redmond, USA). Statistical analysis was performed using IBM SPSS Statistics 23 (IBM Inc., Chicago, IL, USA) and MedCalc (MedCalc Software, Ostend, Belgium).

Results

A total of 1,060 congenital cardiac surgical procedures were performed from January 2010 to December 2017 in our institution (Figure 1). Patients in whom $RcSO_2$ was not available (n = 317) or in whom non-cardiac surgical procedures were performed (n = 40) were not included for further analysis. Eventually, 565 patients were included in the final analysis.

Figure 1: Flow chart depicting the gathering of available data from all cases of pediatric congenital cardiac surgery performed in our institution (2010–2017).
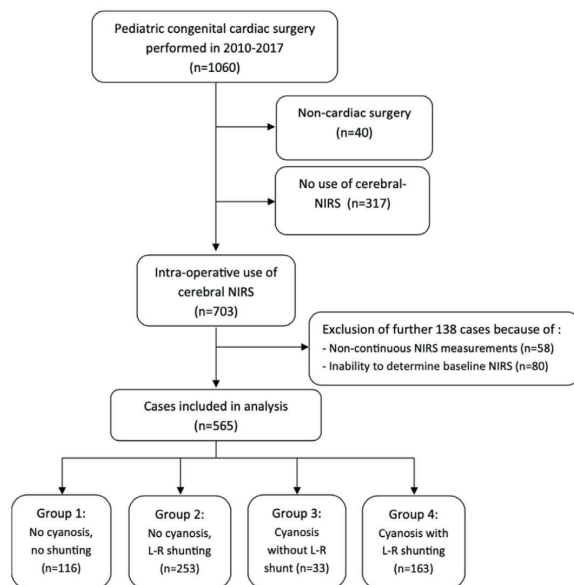
NIRS: near-infrared spectroscopy; L-R: left-to-right

The distribution of patients between the CHD subgroups, as well as their individual diagnoses, is given in Table 1. Patient characteristics and general surgical characteristics are presented in Table 2. The postoperative outcome characteristics of all patients are summarized in Table 3.

Table 1: Cardiac pathology subgroups.

	n
Group 1: No cyanosis, no mixing	
Right ventricle outflow tract obstructions repair of conduit	13
Valve replacement of repair	38
Left ventricle outflow tract obstruction repair	53
Others (Ebstein anomaly, double aortic arch, vessel anomaly, A.lusoria, hypertrophic obstructive cardiomyopathy)	12
Total	*116*
Group 2: Left-to-right shunt without cyanosis	
Atrial septum defect	56
Ventricular septum defect	77
Atrioventricular septum defect	81
Open ductus Botalli	6
Mixed shunting forms	9
Left obstructive with shunting	11
Right obstructive with shunting	4
Valve repair with shunting	10
Total	*254*
Group 3: Cyanosis with left-to-right shunting	
Fontan completion (total cavopulmonary connection)	*33*
Group 4: Cyanosis with left-to-right shunting	
Tetralogy of Fallot	35
Transposition of great arteries	41
Pulmonary atresia with ventricular septum defect	7
Single ventricle circulation: stage 1 and 2	55
Truncus arteriosus communis	5
Total or partial anomalous pulmonary venous return	19
Total	*162*

The distribution and detailed depiction of included diagnoses of all cases included for analysis (n= 565). Given is the absolute number of patients per group.

Table 2: Patient and intraoperative characteristics.

	All cases (n= 565)	Group 1 (n= 116)	Group 2 (n= 253)	Group 3 (n= 33)	Group 4 (n= 163)
Gender, M/F (n)	314/252	68/48	129/124	22/11	95/68
Age (yr)	0.7 [0.3-3.9]	4.6 [0.6-10.5]	1.0 [0.4-3.6]	3.9 [3.3-4.6]	0.3 [0.0-0.6]
Weight (kg)	8 [5-16]	16 [8-31]	9 [5-15]	16 [13-18]	5 [4-8]
Height (cm)	70 [58-103]	107 [69-141]	72 [60-100]	103 [93-110]	58 [50-70]
STS-EACTS score	0.8 (0.7)	0.6 (0.4)	0.6 (0.5)	1.3 (1.3)	1.4 (0.7)
Surgery duration (min)	209 [158-284]	194 [139-293]	181 [140-231]	291 [249-348]	258 [198-321]
CPB time (min	95 [56-151]	89 [0-162]	78 [52-119]	124 [93-180]	124 [79-177]
AoX time (min)	50 [18-85]	44 [17-88]	46 [21-74]	15 [0-66]	65 [19-97]

Continuous data are given as median [interquartile range], except for STS-EACTS, which is given as mean (standard deviation). AoX: aorta cross-clamping; CPB: cardiopulmonary bypass, M: male, F: female; STS-EACTS: Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery

Table 3: Postoperative outcome characteristics.

	All cases (n= 565)	Group 1 (n= 114; 20%)	Group 2 (n= 257; 45%)	Group 3 (n= 33; 6%)	Group 4 (n= 162; 29%)
LOS in ICU (days)	2 [1-7]	1 [1-3]	2 [1-4]	4 [2-9]	6 [3-13]
Prolonged ICU stay	138 (24%)	30 (26%)	60 (23%)	8 (24%)	31 (19%)
Duration of MV (days)	1 [1-2]	1 [1-1]	1 [1-1]	1 [1-2]	2 [1-7]
Prolonged duration of MV	104 (18%)	16 (14%)	51 (20%)	8 (24%)	31 (19%)
LOS in hospital (days)	12 [9-30]	9 [8-38]	10 [9-19]	25 [17-59]	19 [10-32]
Prolonged hospital stay	88 (16%)	11 (10%)	46 (18%)	5 (16%)	32 (20%)
In-hospital mortality	19 (3%)	4 (4%)	4 (2%)	1 (3%)	10 (6%)
30-day mortality	20 (4%)	4 (4%)	5 (2%)	1 (3%)	10 (6%)
One-year mortality	27 (5%)	5 (4%)	7 (3%)	1 (3%)	14 (9%)

Data are given as median [interquartile range]. Prolonged length of stay in ICU, hospital and prolonged duration of MV are defined as a LOS or duration > 3rd quartile of the subgroup of the individual cases (n (% of group)). In-hospital mortality, 30-days mortality and one-year mortality is shown as number (%). ICU: intensive care unit; LOS: length of stay; MV: mechanical ventilation; STS-EACTS: Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery.

Baseline $RcSO_2$

In general, baseline values of $RcSO_2$ (i.e., after tracheal intubation, before surgical incision) were lower in cyanotic patients (group 3 and 4) than in non-cyanotic patients (group 1 and 2): 60% vs 67%, respectively, P < 0.001 (Table 4). There were no further differences in baseline $RcSO_2$ in patients with and without L-R shunting in either non-cyanotic (group 2 vs. group 1, respectively) and cyanotic patients (group 4 vs. group 3, respectively).

Table 4: Intraoperative cerebral oxygen saturation ($RcSO_2$) and $RcSO_2$ desaturation.

	Baseline $RcSO_2$ (%)	Overall intraoperative $RcSO_2$ (%)	$RcSO_2$ AUC below baseline (%*min)	$RcSO_2$ TWA (%)	Total $RcSO_2$ TBBL (min)
All patients	66 [57-74]	65 [59-72]	280 [42-833]	1 [0-4]	50 [13-93]
Non-cyanotic groups					
Group 1 (n= 116)	70 [64-79]	70 [64-77]	285 [35-836]	2 [0-4]	50 [15-95]
Group 2 (n= 253)	67 [58-75]	66 [60-72]	221 [24-688]	1 [0-4]	43 [10-80]
Cyanotic groups					
Group 3 (n= 33)	66 [59-75]	68 [59-75]	644 [194-1267]	2 [1-3]	76 [42-114]
Group 4 (n= 163)	59 [51-68]	61 [55-66]	315 [63-873]	1 [0-4]	57 [17-109]

Data given as median [interquartile range]. AUC: area under the curve, calculated as the product of cerebral desaturations below baseline $RcSO_2$ and time in minutes; TWA: Time-weighted average, calculated as AUC divided by individual duration of surgery; TBBL: time below baseline $RcSO_2$

Baseline $RcSO_2$ was significantly associated with all defined postoperative outcome variables (Table 5), meaning that a lower baseline $RcSO_2$ was associated with an increased odds for the respective outcome variables (LOS in ICU: OR: 0.95; 95% confidence interval [CI]: 0.93 - 0.97; P<0.001. Duration of MV: OR: 0.92; 95% CI: 0.90 - 0.95; P<0.001. LOS in hospital: OR: 0.93; 95% CI: 0.91 - 0.96; P<0.001. 30-day mortality: OR: 0.94; 95% CI: 0.91 - 0.98; P=0.007).

Of note, the cardiac pathology group itself was either not related to outcome (LOS in ICU: OR: 0.85; 95% CI: 0.71 - 1.03, duration of MV: OR: 0.85; 95% CI: 0.69 - 1.05) or was removed from the model (LOS in hospital and 30-day mortality) as it did not improve the model. Baseline $RcSO_2$ showed a stronger association with 30- day mortality than the STS-EACTS score (OR per percentage decrease in baseline $RcSO_2$, 0.94; 95% CI, 0.91 to 0.98; vs OR per unit increase in STS-EACTS score, 1.56; 95% CI, 0.95 to 2.53, respectively).

Table 5: Logistic regression analysis: predictive value for each outcome variable.

Outcome variable		Odds ratio (95% CI)	P
LOS in ICU[a]	Cardiac pathology group	0.85 (0.71 – 1.03)	0.12
	Baseline $RcSO_2$	0.95 (0.93 – 0.97)	< 0.001*
	Intraoperative TBBL $RcSO_2$	1.02 (1.01 – 1.03)	< 0.001*
Duration of MV[b]	Cardiac pathology group	0.85 (0.69 – 1.05)	0.13
	Baseline $RcSO_2$	0.92 (0.90 – 0.95)	<0.001*
	Intraoperative TBBL $RcSO_2$	1.02 (1.01 – 1.03)	0.002*
LOS in hospital[c]	Baseline $RcSO_2$	0.93 (0.91 – 0.96)	<0.001*
	Intraoperative TBBL $RcSO_2$	1.02 (1.01 – 1.04)	<0.001*
30- day mortality[d]	Baseline $RcSO_2$	0.94 (0.91 – 0.98)	0.007**
	Intraoperative TBBL $RcSO_2$	1.03 (1.00 – 1.05)	0.02
	STS-EACTS score[16,17]	1.56 (0.95 – 2.53)	0.08

a: 0.18 (Hosmer-Lemeshow), 0.06 (Cox & Snell), 0.9 (Nagelkerke). Model X^2 (2) = 35, P < 0.001*
b: 0.23 (Hosmer-Lemeshow), 0.09 (Cox & Snell), 0.15 (Nagelkerke). Model X^2 (2) = 54.2, P < 0.001*
c: 0,09 (Hosmer-Lemeshow), 0.08 (Cox & Snell), 0.13 (Nagelkerke). Model X^2 (3) = 42.29, P < 0.001*
d: 0.09 (Hosmer-Lemeshow), 0.08 (Cox & Snell), 0.13 (Nagelkerke). Model X^2 (3) = 42.29, P < 0.001*
* P is considered significant when < 0.0125 (Bonferroni-correction)
** P is considered significant when < 0.01 (Bonferroni-correction)
95% CI = 95% confidence interval; ICU: intensive care unit; LOS: length of stay; MV: mechanical ventilation; $RcSO_2$: cerebral oxygen saturation; TBBL: time below baseline $RcSO_2$.

Intraoperative $RcSO_2$
The data on intraoperative $RcSO_2$ values are presented in Table 4. Overall intraoperative $RcSO_2$ values were lower in cyanotic patients (group 3 and 4) than in non-cyanotic patients (group 1 and 2) (61% vs 66%, respectively; P<0.001).
In 483 patients (86%), $RcSO_2$ decreased below individual baseline values at some time point during surgery, irrespective of the length and degree of desaturation. There were no differences in the incidence of intraoperative $RcSO_2$ desaturations between the subgroups (n= 11, 47, 3, and 21 for group 1-4, respectively).
Cerebral oxygen saturation TWA showed no association with any of the outcome variables (Table 5). Cerebral oxygen saturation TBBL was only weakly associated with the other outcome variables, except 30-day mortality (LOS in ICU: OR: 1.02; 95% CI: 1.01 - 1.03; P<0.001. Duration of MV: OR: 1.02; 95% CI: 1.01 - 1.03; P=0.002. LOS in hospital: OR: 1.02; 95% CI: 1.01 - 1.04; P<0.001).

Prediction of postoperative outcome by baseline $RcSO_2$ and STS-EACTS score
The areas under the ROC curve for the prediction of 30-day mortality by baseline $RcSO_2$ and STS-EACTS was comparable (0.66 [95% CI: 0.55 - 0.76] vs 0.65 [95% CI: 0.54 - 0.77], respectively) and both were significantly different from the reference line (P=0.006 and P=0.007, respectively).

The optimal cut-off baseline RcSO$_2$ value of 60%—as derived by the Youden index—for predicting 30-day mortality was subsequently used as factor in a Kaplan- Meier survival analysis for analyzing one-year mortality. This analysis revealed a substantial difference in mortality: patients with a baseline RcSO$_2$ >60% survived significantly longer than patients with a baseline RcSO$_2$ ≤ 60% (Mantel-Cox [X^2 = 10]; P = 0.001; Figure 2).

Figure 2: Kaplan-Meier survival analysis—comparison between children of a cerebral oxygen saturation above 60% (green line) and below (blue line).

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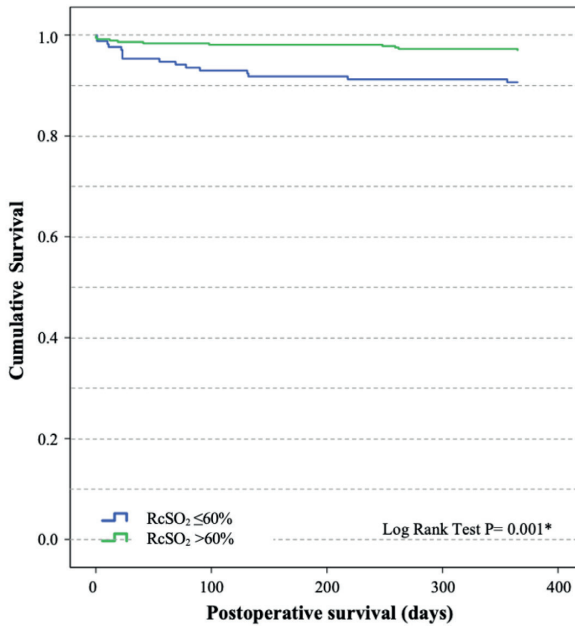
*RcSO$_2$: cerebral oxygen saturation. *P is considered significant when < 0.05.*

Discussion

We investigated the association between intraoperative NIRS-derived $RcSO_2$ and surgical outcome after pediatric CCS performed in our hospital over an eight-year period. In this large historical analysis, lower baseline $RcSO_2$ values—determined after tracheal intubation but before surgical incision—were associated with a longer ICU and hospital stay, as well as with a longer duration of MV, irrespective of the congenital cardiac pathology. Moreover, baseline $RcSO_2$ showed a stronger association with 30-day mortality than the STS-EACTS score did. In contrast, although intraoperative cerebral desaturation occurred frequently in a substantial number of patients, there was no clear association between both the extent and severity of cerebral desaturation and any of the investigated outcome variables.

Baseline $RcSO_2$

Cerebral oxygen saturation monitoring has gained an established role during CCS procedures; however, little is known about its impact on postoperative outcome. Here, we performed a large historical analysis of the association between intraoperative $RcSO_2$ and postoperative outcome in patients that underwent CCS. Also, we included all forms of both cyanotic and non-cyanotic cardiac pathologies while we analyzed outcomes separately per group, accounting for intrinsic between-group differences. For baseline $RcSO_2$, there was a clear association with all of the four investigated outcome variables, i.e., 30-day mortality, LOS in hospital, LOS in the ICU, and length of MV. This finding is only in partial agreement with a recent study[19], as we found an association of baseline $RcSO_2$ with outcome only in cyanotic CHD patients. Of note, in that small retrospective study (n = 59), outcome was defined differently, and was a composite of death, need for renal replacement therapy, use of extracorporeal membrane oxygenation, or increased length of MV or ICU stay. Also, $RcSO_2$ values were lower in cyanotic patients with poor outcome compared with cyanotic patients without poor outcome, while in non-cyanotic patients, no clear association could be found using univariate analysis. In our multivariable logistic regression model, we incorporated the different congenital cardiac conditions as defined previously.[14] Additionally, we used the distribution of primary outcome variables per subgroup (Table 1) to define ''poor outcome'' (i.e., > third quartile of that variable), and hence we were able to provide a more nuanced association between postoperative outcome and CCS, for specific types of CHD, including non-cyanotic (groups 1 and 2) and cyanotic (groups 3 and 4) patients. The latter discrimination is highly relevant, since age and complexity of the surgical procedure are acknowledged predictors of outcome following CCS[1], but are intrinsically linked in the definition(s) of the subgroups, which improves the robustness of our analysis.

It is important to consider that, although the observed association between baseline $RcSO_2$ and outcome was clear, the magnitude of its impact is relatively limited, reflected by ORs between 0.92 and 0.95. It should, however, be reckoned that in a complex setting like CCS, factors influencing outcome are multifactorial.[20] The finding that even an established mortality prediction score like the STS- EACTS score only moderately predicts mortality reflects the complex and multifactorial context of CCS, in which the value of only one variable should not be overemphasized. Nevertheless, baseline $RcSO_2$ values measured after tracheal intubation may at least have some role in identifying those patients at increased risk for adverse postoperative outcome[13,21] —with a stronger association with 30-day mortality than the STS-EACTS score—and can offer a fast and feasible method to serve as an ''early warning tool'', either intraoperatively or in the early postoperative phase.[22–26]

Hence, baseline RcSO$_2$— determined after tracheal intubation—may guide in clinical routing and pre-emptive cardiopulmonary optimization and risk-stratification. Future studies should evaluate this issue further.

Importantly, as shown previously in adult patients undergoing cardiac surgery[21], low RcSO$_2$ values (i.e., <50%) were associated not only with neurologic adverse outcome but also with increased mortality rates. Therefore, as stated in an accompanying editorial[27], the brain might be an ''index organ'', reflecting the severity of cardiopulmonary compromise in the individual patient. The observations on baseline RcSO$_2$ in our study confirm that this statement might apply to pediatric patients undergoing CCS, even when corrected for the baseline differences in RcSO$_2$ per cardiac pathology group.

The definition of a baseline RcSO$_2$ value for the population of pediatric CHD patients is debatable, in the context of evaluating its association with intra- and postoperative hemodynamic management and outcome. The observed differences in baseline RcSO$_2$ values between cyanotic and non-cyanotic patients (60% vs. 67%, respectively) were typical and as expected for these populations.[14] In this context, it is important to consider that we determined baseline values under general anesthesia after tracheal intubation, before surgical incision. This time period was chosen for determining baseline values because hemodynamics and FiO$_2$ were both stable. In addition, the previous stress around induction of anesthesia has had time to subside. Also, we speculate that setting a baseline condition (i.e., RcSO$_2$) under general anesthesia is more likely to resemble physiologic conditions in the perioperative phase (including the postoperative ICU phase); e.g., cerebral oxygen delivery and consumption of an awake pediatric patient in the ward a day before surgery might be substantially different than under conditions in the surgical or ICU setting. As such, directing RcSO$_2$ monitoring and treatment upon RcSO$_2$ obtained during stable conditions in an equivalent setting might yield more realistic treatment goals for postoperative hemodynamic management. Nevertheless, to our knowledge, the association between pre- and post- induction RcSO$_2$ has not been documented previously, neither has the association of both of these values with postoperative outcome. This issue on ''personalized'' goal-directed hemodynamic management requires further elucidation in future trials.

Intraoperative RcSO$_2$ desaturations
In contrast to our observation on the importance of baseline RcSO$_2$ on outcome, we found only a minimal association between intraoperative RcSO$_2$ decrease and outcome—only for the length of cerebral desaturation periods intraoperatively, and not for its severity (low values). This observation is surprising, as in a substantial number of patients (>80%), RcSO$_2$ values did decrease below their individual baseline at least some point during surgery, and it was shown that intraoperative cerebral desaturations are associated with reduced postoperative neurologic functioning.[28,29] Another study in infants showed abnormalities in psychomotor development and brain magnetic resonance imaging, one year after surgery, in those patients with perioperative periods of diminished cerebral oxygen delivery.[30] A more recent multicentre international study measuring the incidence of low regional cerebral oxygenation using NIRS in infants during anesthesia for non-cardiac surgery found that mild and moderate cerebral and arterial desaturations occur frequently, but they were unlikely associated with learning and behavioral abnormalities.[31]

An important consideration is that the attending anesthesiologist was not blinded to $RcSO_2$ readings. In fact, $RcSO_2$ monitoring was intentionally applied and was actually used, together with measurement of other variables such as mean arterial pressure and $etCO_2$, for guiding hemodynamic management. Hence, an assumed association between intraoperative $RcSO_2$ desaturation and postoperative outcome is likely to be blunted to some extent, as intraoperative management may have prevented more serious $RcSO_2$ desaturations than those observed, also by additional interventions such as the transfusion of blood and the monitoring of other vital aspects, e.g., processed electroencephalographic depth-of-anesthesia monitoring, cardiac ultrasound, etc. Hence, the true association between (temporal) decreases in $RcSO_2$ and outcome might be underemphasized in our study given that it is likely that in case of $RcSO_2$ decreases, prompt action(s) were taken for correction, maybe even before actual desaturation occurred; e.g., in another setting in low birth weight patients (n = 59) who were randomized to receive either dopamine or epinephrine, distinct drug-related changes were seen in cerebral hemodynamics[32], while in another study[33] intraoperative $RcSO_2$ desaturations were linked with concomitant drops in mean arterial blood pressure. Like in adult cardiac surgery[34], a prospective validation of the use of continuous $RcSO_2$ monitoring—and the effects of vasopressors and/or inotropes in optimizing $RcSO_2$ and improving outcome in CCS—is still required.

Study limitations
First, this study is a historical cohort study with all the inherent disadvantages; e.g., in most cases $RcSO_2$ was measured unilaterally, while bilateral readings were obtained in all cases in the ideal setting. The choice whether $RcSO_2$ was measured uni- or bilaterally was, however, made by the attending anesthesiologist, most likely depending on patient characteristics and personal preference, as there is no uniform agreement when to assess $RcSO_2$ uni- or bilaterally.[35–37] Also, while the analysis was based on historical data and outcome variables that were defined a priori or before study initiation, we only assessed lengths of stay, duration of MV, and mortality—not direct measures of neurologic functioning according to uniform definitions.[38]
Second, our regression model was constructed to identify the strength of the association between NIRS- derived $RcSO_2$ values and outcome variables using a stepwise logistic regression model. In addition, the use of stepwise regression models like the one used in this study may suffer from substantial limitations described elsewhere[39,40], which may result in an ''overestimation'' of the observed associations and their robustness. Given that in this exploratory study was derived from a relatively large data set, for which only five or fewer predictors were defined, the influence of these limitations on the outcome of our analysis is substantially reduced, although it is unknown to what extent. The additional influence of residual confounding, i.e., other variables that are not taken into account but simultaneously affect outcome variables, cannot be determined based on the analysis that we performed. For example, age is intrinsically involved in the underlying cardiac pathology, the indication for CCS, and supposedly, in the risk of morbidity and mortality itself, but was not included in the model itself.[14]

Third, the $RcSO_2$ AUC relative to baseline was calculated using an automated algorithm after elimination of artefacts. Here, the accuracy of the AUC and its derived variable (TWA) is as ''good'' as the data on which it is based, and is primarily dependent on the availability of $RcSO_2$ in a high frequency. For instance, a gap of $RcSO_2$ data availability for 30 sec indicated that $RcSO_2$ was stable for that time period, and AUC calculations were based on these interpolated values.

Fourth, we have not investigated postoperative values of $RcSO_2$. Various studies have looked at these values and their relation with postoperative outcome, at least during the first 24-48hr after CCS during stay on the ICU stay.[11,41–43] It was shown in these studies that children with low $RcSO_2$ values were hospitalized longer and suffered more complications, including neurologic impairment than children with higher values did. In one study[11], the mean cerebral NIRS of less than 56% over the first 48hr after surgery yielded a sensitivity of 75% and a specificity of 79% to predict those at risk for subsequent adverse events. In adults[29], the incidence of prolonged cerebral desaturation is significantly higher in patients with cognitive decline. It was suggested to implement NIRS as a standardized tool for monitoring $RcSO_2$ in the postoperative period, since time points such as right after weaning from CPB or a few hours postoperatively helped in predicting complications in the early postoperative phase.[41,42,44,45] Finally, a study in healthy adults showed that $RcSO_2$ readings can be affected by extracranial ''contamination'', suggesting that $RcSO_2$ does not solely reflect cerebral oxygenation.[46] This issue has, however, not yet been studied in pediatric patients, and it is unknown to which extent this might have impacted the observed associations in our study.

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Conclusion
A low baseline cerebral oxygen saturation measured after tracheal intubation and before surgical incision was associated with adverse postoperative outcomes in pediatric patients undergoing CCS, while the length of intraoperative cerebral desaturation was only minimally associated with postoperative outcome. Surprisingly, the severity of intraoperative cerebral desaturation was not associated with postoperative outcome. Furthermore, baseline $RcSO_2$ values predicted mortality to some extent, equivalent to the already established STS-EACTA score. Therefore, measuring baseline $RcSO_2$ after tracheal intubation, might help identify patients at increased perioperative risk.

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