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ORIGINAL ARTICLE

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S100B and its relation to cerebral oxygenation in neonates and infants undergoing surgery for congenital heart disease

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Abstract

Objectives: Neonates and infants undergoing surgery for congenital heart disease are at risk for developmental impairment. Hypoxic-ischemic brain injury might be one contributing factor. We aimed to investigate the perioperative release of the astrocyte protein S100B and its relation to cerebral oxygenation.

Methods: Serum S100B was measured before and 0, 12, 24, and 48 hours after surgery. Cerebral oxygen saturation was derived by near-infrared spectroscopy. S100B reference values based on preoperative samples; concentrations above the 75th percentile were defined as elevated. Patients with elevated S100B at 24 or 48 hours were compared to cases with S100B in the normal range. Neonates (≤28 days) and infants (>28 and ≤365 days) were analyzed separately due to age-dependent release of S100B.

Results: Seventy-four patients underwent 94 surgical procedures (neonates, $n = 38$; infants, $n = 56$). S100B concentrations were higher in neonates before and after surgery at all time points ($P \leq .015$). Highest values were noticed immediately after surgery. Postoperative S100B was elevated after 15 (40.5%) surgeries in neonates. There was no difference in pre-, intra-, or postoperative cerebral oxygenation. In infants, postoperative S100B was elevated after 23 (41.8%) procedures. Preoperative cerebral oxygen saturations tended to be lower (53 ± 12% vs 59 ± 12%, $P = .069$) and arterial-cerebral oxygen saturation difference was higher (35 ± 11% vs 28 ± 11%, $P = .018$) in infants with elevated postoperative S100B. In the early postoperative course, cerebral oxygen saturation was lower (54 ± 13% vs 63 ± 12%, $P = .011$) and arterial-cerebral oxygen saturation difference was wider (38 ± 11% vs 30 ± 10%, $P = .008$). Cerebral oxygen saturation was also lower for the entire postoperative course (62 ± 18% vs 67 ± 9%, $P = .047$).

Conclusions: Postoperative S100B was elevated in about 40% of neonates and infants undergoing cardiac surgery. Infants with elevated postoperative S100B had impaired perioperative cerebral tissue oxygenation. No relation between S100B and cerebral oxygenation could be demonstrated in neonates.

KEYWORDS

brain biomarkers, cardiopulmonary bypass, cerebral protection, near-infrared spectroscopy

1 | INTRODUCTION

Within the past decades, advances in surgical technique and perioperative care have led to a substantial increase in survival for children with congenital heart disease (CHD). Despite these improvements, children with CHD are still at higher risk for neurodevelopmental impairment.[1] Developmental problems, including cognitive impairment, fine and gross motor deficits, and speech and language disorders, are common especially in children with complex CHD requiring corrective or palliative surgery during the neonatal period.[1-4] However, cognitive abnormalities, often to a milder degree, are also found in children with less complex CHD undergoing surgery beyond the neonatal period.[1,5-8]

Developmental impairment observed in children with CHD is multifactorial and is influenced by nonmodifiable patient-specific factors and potentially modifiable factors including surgical technique and perioperative care. Abnormal findings on magnetic resonance imaging (MRI) suggestive of cerebral ischemia, mainly white matter injury, have been reported particularly in neonates with CHD before and after surgery.[9-16] Therefore, perioperative hypoxic-ischemic brain injury might be a relevant modifiable cause. Brain injury after surgery for CHD in newborns and infants is usually subtle and subclinical. As developmental assessment can be performed with a relatively long period of latency only, the identification of early postoperative parameters permitting the identification of patients at risk or even predicting long-term developmental outcomes are of special interest. MRI is capable to detect hypoxia-ischemic lesions but is challenging for routine monitoring, especially in the early postoperative period or if repeated studies are necessary. Near-infrared spectroscopy (NIRS) allows noninvasive and real-time measurement of cerebral tissue oxygen saturation and is frequently used for perioperative monitoring of patients with CHD. Previous studies have reported relationships between abnormal findings on MRI, cerebral oxygenation, and neurodevelopmental outcomes.[14,15,17-19] A brain-specific biomarker released into the bloodstream after cellular damage would be of great value for clinical practice. Among others, the astrocyte protein S100B has previously been intensively studied. S100B is a small, dimeric, cytosolic calcium-binding protein, which predominantly occurs in astrocytes. Its exact biological role is still under debate. Release of S100B into the blood may occur due to astrocyte injury as well as due to blood-brain barrier dysfunction.[20] Elevated S100B serum levels have been proposed as a biomarker of various pathological cerebral conditions after cardiac surgery in adults.[20] In neonates with perinatal hypoxic-ischemic encephalopathy, S100B levels were related to neurological outcome.[21] However, the value of S100B as a reliable marker for developmental outcome after cardiac surgery in neonates and infants is unclear. S100B has been associated with acute adverse neurologic outcome, but so far, there is only one study which showed a relation between S100B values and developmental outcome after cardiac surgery in early infancy.[22-24]

The aim of this prospective cohort study was to determine perioperative S100B levels in neonates and infants undergoing surgical repair of CHD with cardiopulmonary bypass. In contrast to previous studies, we defined normal and pathological values of S100B and evaluated the association between S100B levels and cerebral tissue oxygenation assessed by NIRS, which have not been evaluated together before. Our hypothesis was that higher serum levels of S100B relate to impaired cerebral tissue oxygenation. In addition, the relation between S100B concentrations, variables related to surgical treatment and routine postoperative monitoring data was of interest.

2 | METHODS

Neonates and infants with CHD up to 12 months of age undergoing surgery with cardiopulmonary bypass were eligible for enrollment. Exclusion criteria included proven or clinically suspected genetic syndrome, weight at surgery of less than 2500 g, history of birth asphyxia or preexisting brain injury and proven or suspected brain injury on routine preoperative head ultrasound. The study was reviewed and approved by the local Institutional Review Board. Written informed consent was provided for all subjects.

All patients received standard care during the perioperative period. In terms of CPB management, the pH-stat method was used for cooling if moderate or deep hypothermia was utilized. Neonates undergoing the Norwood procedure were operated on with selective cerebral perfusion during reconstruction of the aortic arch. Hemofiltration was routinely used before weaning from CPB in neonates and infants.

2.1 | S100B

Serum levels of S100B were obtained before surgery as well as 0, 12, 24, and 48 hours after surgery. Blood was drawn from indwelling arterial or central venous lines in 1 cc serum separator tubes. Samples were centrifuged and directly analyzed or aliquots were stored for short-term at −20°C until analysis. Serum levels of S100B were determined by electrochemiluminescence immunoassay (Elecsys, Roche, Mannheim, Germany). This assay detects the beta subunit of both isoforms of S100B (heterodimer S100A1B and homodimer S100BB). This analysis was routinely offered by the hospital laboratory.

Serum levels of S100B in healthy children are known to be age-dependent with highest values in neonates.[25,26] For the current study, reference values for the cohort were defined based on preoperative S100B levels. S100B concentrations >75th percentile were defined as elevated. Two subgroups, neonates (age ≤28 days) and infants (age >28 days and ≤365 days), were analyzed separately.

Within both groups associations between S100B levels and the underlying cardiac diagnosis were evaluated. For neonates S100B levels were compared between patients with single ventricle physiology and cases eligible for biventricular repair (representing patients without cyanosis after surgery). In infants, S100B levels were compared between patients with or without cyanotic CHD. Due to the possible influence of lower postoperative arterial

oxygen saturation on NIRS values in patients with persisting postoperative cyanosis, a subgroup analysis was performed including only infants without or with abolished cyanosis after corrective surgery.

The kinetic of S100B release after surgeries for CHD has been previously described. Peak S100B concentrations are typically observed directly after surgery, a return to baseline values within 24 to 72 hours has been reported.[22,23] For the actual study we compared patients with elevated S100B at 24 or 48 hours and cases with S100B in the normal range. In addition, absolute S100B values were discussed in comparison with currently available reference data.[25,26]

2.2 | Near-infrared spectroscopy and routine monitoring

Routine perioperative monitoring included continuous measurement of arterial oxygen saturation (SaO_2) and invasive arterial and central venous blood pressure (IntelliVue, Philips Healthcare, Best, The Netherlands). Arterial blood gases were obtained at 1-2 hour intervals; central venous blood gases from the superior vena cava were sampled at 4-hour intervals for the first 48 postoperative hours. Lactate levels were analyzed together with arterial blood gases. Early postoperative and maximal lactate concentrations were determined.

NIRS probes were placed on the patient's midline forehead and slightly to the right of midline on the T10-L2 posterior flank. Cerebral (ScO_2) and somatic tissue oxygen saturations (SsO_2) were monitored continuously (INVOS 5100, Medtronic, Minneapolis, Minnesota). NIRS data was stored digitally with a sampling rate of every 3 seconds. NIRS raw data was transferred into a custom-made database system and average values over 30 seconds were calculated. NIRS values were matched to hemodynamic and respiratory data for 12 hours preoperatively and for 48 hours postoperatively. Mean values were calculated for the 12 preoperative hours (baseline), for the first 4 postoperative hours (early postoperative course), and for the entire 48 hour postoperative period. The intraoperative period was divided into five periods (prebypass, cooling, low-flow, rewarming, and off-pump) and mean values were calculated for each period and the entire intraoperative course.

To define periods of diminished ScO_2, a lower threshold of 40% was chosen. The area under the curve of ScO_2 values <40% was calculated to indicate the extent of desaturation below the threshold of 40% (AUC40 ScO_2). To estimate cerebral oxygen extraction, the difference between corresponding SaO_2 and ScO_2 measurements was calculated ($\Delta SacO_2 = SaO_2 - ScO_2$).

2.3 | Statistics

Continuous variables are expressed as mean and standard deviation or median and interquartile range as appropriate and categorical data as count and percentages. We employed Fisher's exact test for analysis of categorical data. Continuous variables were compared with the Student's *t* test for two independent samples or with the Mann-Whitney U test in case of nonnormally distributed data. Correlations were calculated using the Pearson correlation coefficient. All statistical analyses were performed with the statistical software package SPSS (IBM SPSS Statistics for Windows, Version 22.0; IBM Corp., Armonk, New York). A value of $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Patients

Between May 2015 and September 2016, 74 patients (36 neonates and 38 infants) were enrolled in the study. The underlying diagnosis of patients enrolled is given in Table 1. The majority of neonates had cyanotic CHD (neonates, $n = 32$ and infants, $n = 22$). The diagnosis was made prenatally in 30 (40.5%) patients. Overall 11 (14.9%) patients were born preterm, with only 2 undergoing surgery within the newborn period. The median gestational age was 39.1 (37.6-40.0) weeks. Extracardiac malformations were seen in 9 (12.3%) cases.

Prior to enrollment, 4 neonates had undergone pulmonary artery banding and another 4 balloon atrial septostomy. With one exception, all neonates received prostaglandin E1 infusion for maintaining ductal patency. Preoperative adverse events were noted in 6 cases including clinical deterioration with signs of multiorgan failure, the need for intubation or inotropic support, unplanned cardiac surgery, or intervention.

In those enrolled beyond the neonatal period, 9 patients had undergone previous surgery without cardiopulmonary bypass (shunt placement, $n = 7$; pulmonary artery banding, $n = 2$). Catheter interventions had been performed in 7 patients (balloon atrioseptostomy, $n = 4$; balloon valvuloplasty of the pulmonary valve, $n = 1$; arterial duct stenting, $n = 1$; balloon angioplasty aortic isthmus, $n = 1$). Two patients still received prostaglandin E1 infusion at enrollment. Preoperative adverse events were noted in 2 cases.

TABLE 1 Cardiac diagnosis

Hypoplastic left heart syndrome and variants	17 (23.0%)
Other single ventricle lesions	7 (9.5%)
Transposition of the great arteries	14 (18.9%)
Tetralogy of Fallot	10 (13.5%)
Ventricular septal defect	9 (12.3%)
Ventricular septal defect +aortic arch abnormality[a]	5 (6.8%)
Common arterial trunk	4 (5.4%)
Total anomalous pulmonary venous drainage	2 (2.7%)
Others[b]	6 (8.1%)

[a]Interrupted aortic arch ($n = 1$) and coarctation ($n = 4$).
[b]Atrial septal defect, atrioventricular septal defect, pulmonary valve stenosis, aortic valve stenosis, Bland-White-Garland syndrome, partial anomalous pulmonary venous drainage with ventricular septal defect.

TABLE 2 Surgical data and postoperative course

	Neonates (n = 38)	Infants (n = 56)	P value
Type of surgery	Norwood procedure (n = 15)	SCPA (n = 21)	
	Arterial switch operation (n = 12)	Repair tetralogy of Fallot (n = 10)	
	VSD closure +arch repair (n = 4)	VSD closure (n = 9)	
	Repair common arterial trunk (n = 2)	Aortic arch repair (n = 3)	
	Others[a] (n = 5)	Others[b] (n = 13)	
Surgical data			
Age at surgery (days)	5 (3-7)	128 (89-191)	<.001
Weight at surgery (kg)	3.42 ± 0.44	6.14 ± 1.40	<.001
Cardiopulmonary bypass (min)	139 ± 37	118 ± 38	.009
Aortic cross-clamp (min)[c]	68 ± 30	76 ± 30	.287
Ventricular fibrillation (min)[d]	23 ± 17	61 ± 27	na
Selective cerebral perfusion (min)[e]	43 ± 12	27 ± 9	na
Temperature nadir (°C)	22.0 ± 4.3	28.6 ± 2.6	<.001
Primary chest closure (n)	32 (84.2%)	55 (98.2%)	.016
Postoperative course			
Mechanical ventilation (h)	87 (61-118)	15 (4-68)	<.001
Duration of inotropic support (h)	26 (18-73)	5 (0-31)	.002
Intensive care unit stay (days)	11 (6-33)	5 (3-7)	<.001
Hospital stay (days)	25 (12-49)	9 (7-16)	.001

Abbreviation: na, not applicable.

[a]Aortic arch reconstruction and PA-banding (n = 2), repair of anomalous pulmonary venous return (n = 2), atrioseptectomy and PA-banding (n = 1).

[b]Arterial switch operation (n = 2), repair of truncus arteriosus (n = 2), shunt/conduit replacement (n = 3), repair of anomalous pulmonary venous return (n = 1), ASD-closure (n = 1), AVSD repair (n = 1), pulmonary valve reconstruction (n = 1), aortic valve reconstruction (n = 1), coronary artery transfer (n = 1).

[c]Aortic cross-clamp: neonates, n = 36 vs infants, n = 33.

[d]Ventricular fibrillation: neonates, n = 3 vs infants, n = 20.

[e]Selective cerebral perfusion: neonates, n = 19 vs infants, n = 2.

3.2 | Surgeries

The 74 patients underwent a total of 94 surgical procedures utilizing cardiopulmonary bypass. Of those, 38 were performed in neonates and 56 procedures took place beyond the neonatal period. The Norwood procedure and the arterial switch operation were the 2 surgeries most frequently performed in the group of neonates. In infants, the creation of a superior cavopulmonary anastomosis (SCPA) was the most common procedure. Surgical data is given in Table 2. Duration of postoperative mechanical ventilation, inotropic support and length of stay in the intensive care unit and total hospital stay were longer after surgeries in neonates compared to infants (Table 2). Postoperative complications were noted after 34 (36.0%) surgeries, the frequency was not different between neonates and infants. Clinically overt neurological injury occurred in 1 patient only, who had an embolic stroke 10 days after SCPA. Two patients died within the study period. The first patient 91 days after the Norwood procedure due to shunt thrombosis, the second due to intractable heart failure 28 days after a biventricular repair approach in a case with borderline left heart structures.

3.3 | S100B serum concentrations

Figure 1 shows pre- and postoperative S100B serum concentrations in neonates and infants. Mean S100B concentrations were higher in neonates before and after surgery at all time points ($P \leq .015$). In both groups, highest S100B values were noticed immediately after surgery. Postoperative values declined and were not significantly different from preoperative concentrations after 12 hours in neonates and after 48 hours in infants.

For the current study S100B reference values were defined based on preoperative samples. Serum concentrations above the 75th percentile were defined as elevated. Thresholds were defined separately for neonates (P75th 0.33 µg/L) and infants (P75th 0.23 µg/L).

3.4 | S100B in the preoperative period

In neonates, preoperative S100B was above the 75th percentile in 8 patients. Highest values (outliers and extreme values, Figure 1) were seen in 4 patients with HLHS or other functional single ventricle lesions with obstructed systemic outflow. The mean preoperative S100B concentration was not different between patients with single ventricle physiology and patients eligible for biventricular repair (0.34 ± 0.17 µg/L vs 0.30 ± 0.11 µg/L, P = .344).

In infants, preoperative S100B was elevated in 11 cases, 5 had single ventricle physiology. There was no difference in preoperative S100B concentrations between cyanotic or noncyanotic infants (0.19 ± 0.09 µg/L vs 0.18 ± 0.06 µg/L, P = .806).

3.5 | S100B in the immediate postoperative course

In neonates, S100B concentrations immediately after surgery ranged between 0.21 and 7.00 µg/L. Mean S100B after the Norwood procedure was 1.47 ± 1.70 µg/L compared to 0.89 ± 0.45 µg/L in those after biventricular repair (P = .209). S100B values were negatively correlated to weight at surgery (r = −0.417, P = .010). There was no correlation between S100B and duration of cardiopulmonary bypass or aortic cross-clamp in neonates.

In infants, S100B values immediately after surgery were between 0.26 and 2.03 µg/L. There was no difference in S100B

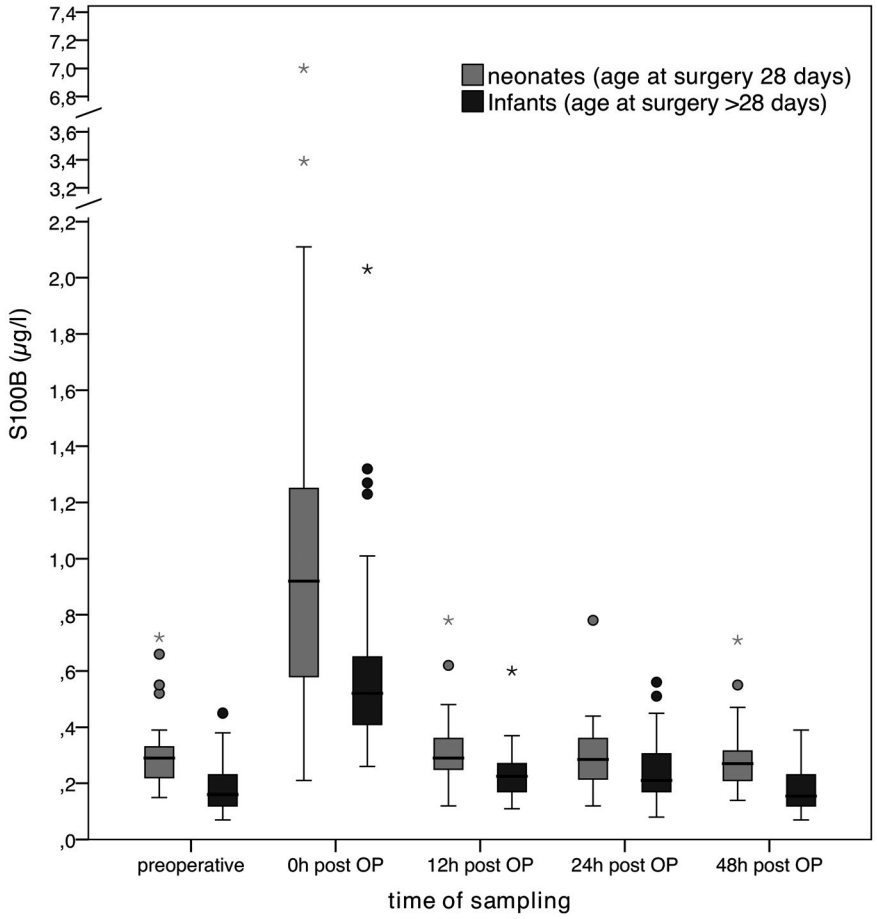

FIGURE 1 Perioperative S100B serum concentrations in neonates and infants. Whiskers above and below the box represent the largest and smallest data points that are <1.5 box lengths (interquartile range) away from the end of the box. Circles highlight data points >1.5 box lengths (outliers) and asterisks data points >3 box lengths away (extreme values). S100B concentrations were higher in neonates before and after surgery at all time points ($P \leq .015$)

levels between cyanotic or noncyanotic infants (0.61 ± 0.34 µg/L vs 0.60 ± 0.29 µg/L, $P = .874$). Immediate postoperative S100B concentrations were weakly to moderately correlated with age ($r = -0.324$, $P = .018$), weight at surgery ($r = -0.425$, $P = .001$) and the duration of cardiopulmonary bypass ($r = 0.407$, $P = .003$).

In both groups, intraoperative ScO_2 and SsO_2 values were not correlated to postoperative S100B concentrations obtained immediately after surgery.

3.6 | Elevated S100B in neonates

Postoperative S100B at 24 or 48 hours was still elevated after 15 (40.5%) surgeries in neonates. In those, S100B concentrations were between 0.34 and 0.78 µg/L (mean: 0.42 ± 0.11 µg/L). There was no difference in terms of surgical data in comparison between cases with normal and elevated postoperative S100B (Table 3). The frequency of patients with elevated S100B and underlying single ventricle physiology was not different from those undergoing biventricular repairs (7/15 vs 8/22, $P = .734$).

Preoperative, intraoperative, and postoperative cerebral tissue oxygen saturations for neonates are displayed in Figure 2A. Preoperative ScO_2 was not different between cases with and without elevated S100B. Intraoperative ScO_2 values were not different for the entire course or for any of the intraoperative periods (Table 4, Figure 2A). There was no difference in postoperative ScO_2 measurements between cases with elevated and those with S100B concentrations in the normal range. Mean SsO_2 of the pre-, intra-, and postoperative course was not different either (Table 4).

Comparison of routine monitoring data is shown in Table 4. In the preoperative course, the arterial partial pressure of oxygen (pO_2) was lower in cases with elevated S100B in the postoperative course. Lactate concentrations in the early postoperative course and maximum lactate of the entire postoperative period were higher in cases with S100B above the 75th percentile. There was a positive correlation between early postoperative lactate levels and S100B values 24 hours after surgery ($r = 0.444$, $P = .007$).

The frequency of postoperative complications was not different between cases with elevated postoperative S100B and those with values in the normal range (6/15 vs 8/22, $P = .546$). No difference was found for the median length of postoperative ventilation (86 (53-109) vs 95 (66-124) hours, $P = .276$) or the duration of inotropic support (22 (18-88) vs 35 (18-73) hours, $P = .796$).

3.7 | Elevated S100B in infants

In infants, postoperative S100B at 24 or 48 hours was elevated after 23 (41.8%) procedures. In those, S100B concentrations were between 0.26 µg/L and 0.56 µg/L (mean: 0.35 ± 0.08 µg/L). Age

TABLE 3 Surgical data

	Neonates			Infants		
	S100B < P75th (*n* = 22)	S100B > P75th (*n* = 15)	*P* value	S100B < P75th (*n* = 32)	S100B > P75th (*n* = 23)	*P* value
Age (days)	5 (3-7)	4 (2-6)	.775	130 (103-231)	125 (79-146)	.665
Weight (kg)	3.52 ± 0.46	3.28 ± 0.40	.110	6.44 ± 1.54	5.80 ± 1.12	**.046**
CPB (min)	133 ± 39	148 ± 34	.229	112 ± 38	125 ± 38	.202
ACC (min)	64 ± 28	71 ± 32	.497	70 ± 30	86 ± 29	.139
ACP (min)	41 ± 10	44 ± 15	.620	27 ± 9	na	na
Ind. V. fib. (min)	na	na	na	55 ± 33	68 ± 18	.288
Temp. nadir (°C)	22.8 ± 4.9	21.2 ± 3.3	.256	28.9 ± 2.9	28.3 ± 2.3	.400

Bold value indicates statistical significance.
Abbreviations: CPB, cardiopulmonary bypass; ACC, aortic cross-clamp; ACP, antegrade cerebral perfusion; Ind. V. fib, induced ventricular fibrillation; na, not applicable.

at surgery was not different between cases with normal and elevated postoperative S100B concentrations, but weight at surgery was lower (Table 3). No differences were found for the duration of cardiopulmonary bypass, aortic cross-clamp or induced ventricular fibrillation (Table 3). Preoperative ScO_2 tended to be lower and $\Delta SacO_2$ was higher in cases with elevated S100B, while no difference was found for SsO_2 (Figure 2B, Table 4). Mean ScO_2 and SsO_2 values for the entire intraoperative course were not significantly different (Table 4, Figure 2B). ScO_2 tended to be lower during cooling (58 ± 12% vs 64 ± 10%, *P* = .055) and low-flow CPB (56 ± 11% vs 62 ± 13%, *P* = .095) (Figure 2B).

In the postoperative course, ScO_2 and SsO_2 were lower and $\Delta SacO_2$ was wider in cases with elevated postoperative S100B (Table 4, Figure 2B). Lactate concentrations immediately after surgery and maximal concentrations were higher compared to those with S100B in the normal range (Table 4). There was a positive correlation between initial lactate levels and S100B values at 0, 12, and 24 hours after surgery, which was strongest for S100B levels after 24 hours (*r* = 0.449, *P* = .001).

The median length of postoperative ventilation was not different between cases with or without elevated postoperative S100B (16 (4-127) vs 15 (5-44) hours, *P* = .739), but duration of inotropic support was longer in those with elevated S100B (22 (5-91) vs 1 (0-15) hours, *P* = .001). The frequency of postoperative complications was higher in those with elevated postoperative S100B (14/23 vs 5/32, *P* = .001). Mean S100B concentrations of patients with and without postoperative complications were only different at 24 hours after surgery (0.30 ± 0.12 μg/L vs 0.20 ± 0.09 μg/L, *P* = .007).

3.8 | Elevated S100B in noncyanotic infants or infants with abolished cyanosis after surgery

The subgroup of infants without or with abolished cyanosis after corrective surgery included 31 cases (tetralogy of Fallot, *n* = 10; ventricular septal defect, *n* = 9; common arterial trunk, *n* = 3; transposition of the great arteries, *n* = 2; others, *n* = 7). Median age at surgery tended to be younger in cases with elevated postoperative S100B (189 (102-243) days vs 117 (77-141) days, *P* = .085). Preoperatively, no difference was seen for ScO_2, but $\Delta SacO_2$ was wider in those with elevated postoperative S100B (27 ± 9% vs 34 ± 9%, *P* = .033). Intraoperative ScO_2 was lower on bypass during cooling and low-flow CPB in cases with elevated S100B (Cooling: 57 ± 10% vs 64 ± 8%, *P* = .043; low-flow: 53 ± 9% vs 62 ± 9%, *P* = .020). Mean ScO_2 was lower and $\Delta SacO_2$ was higher during the early (ScO_2: 68 ± 9% vs 59 ± 10%, *P* = .013; $\Delta SacO_2$: 32 ± 10% vs 42 ± 10%, *P* = .005) and for the entire postoperative course (ScO_2: 73 ± 5% vs 68 ± 5%, *P* = .008; $\Delta SacO_2$: 26 ± 5% vs 32 ± 5%, *P* = .004) in cases with elevated postoperative S100B. SsO_2 was not different. No association between postoperative lactate levels and S100B could be demonstrated.

4 | DISCUSSION

This study showed that infants beyond the neonatal period with elevated postoperative S100B concentrations after cardiac surgery utilizing cardiopulmonary bypass have impaired perioperative cerebral tissue oxygenation in terms of lower absolute cerebral NIRS values or a wider arterial-cerebral saturation difference, an estimate of cerebral oxygen extraction. Our hypothesis, that postoperative S100B levels are related to perioperative cerebral oxygenation assessed by NIRS could not be proven in neonates. In both, neonates and infants, postoperative S100B concentrations were associated with lactate levels, a nonspecific marker of tissue injury.

The protein S100B has been previously studied as a potential biomarker for brain injury in neonates and infants undergoing cardiac surgery for CHD, however, the association between perioperative cerebral tissue oxygenation and S100B has not been reported.[22,23,27-29] In contrast to previous studies, we defined elevated S100B concentrations to evaluate the impact of cerebral oxygenation and other variables related to surgical treatment and perioperative management on S100B release.

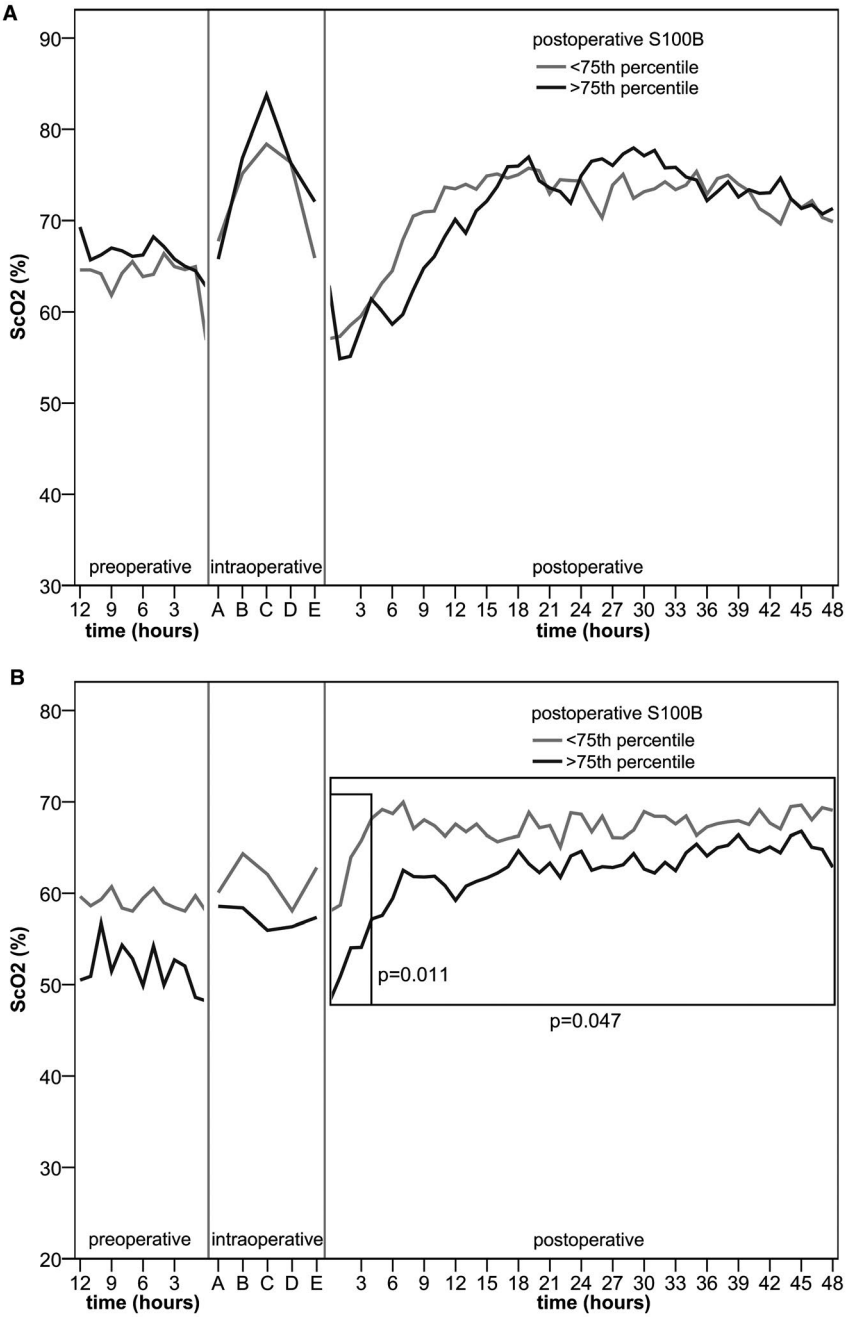

FIGURE 2 Pre-, intra-, and postoperative cerebral tissue oxygen saturations (ScO_2) in neonates (A), infants (B) in comparison between cases with postoperative S100B values above and below the 75th percentile. The intraoperative period was divided into five periods, prebypass (A), cooling (B), low-flow (C), rewarming (D), off pump (E). *P* values refer to the comparison of mean values between groups in the outlined perioperative period

4.1 | Preoperative S100B

Preoperative S100B concentrations were higher in neonates compared to infants. Serum S100B levels in apparently healthy children are known to be related to age and S100B values have to be interpreted based on age-dependent reference values. Highest concentrations with a relatively wide range are seen in neonates.[25,26] Among others, this might be explained by the immaturity of the blood-brain-barrier. Higher S100B levels in neonates with CHD compared to infants with CHD are therefore unlikely explained by underlying cerebral injury. However, in patients with S100B values above certain thresholds, astrocyte injury also needs to be considered. In our neonates with CHD, 4 had preoperative S100B values above the 95th percentile (>0.53 µg/L) based on recently published reference values for healthy children.[26] All had functional single ventricle physiology with obstructed systemic outflow. In neonates with complex CHD such as HLHS, preoperative brain injury on MRI is a common finding and elevated S100B values might be related to impaired cerebral oxygen delivery.[9-12,16]

4.2 | Postoperative S100B

The release of S100B after surgery for CHD follows a distinct pattern, which has been shown in varying cohorts of patients. Highest S100B concentrations were typically seen immediately after cardiopulmonary bypass and concentrations normalized to preoperative

TABLE 4 NIRS and routine monitoring data

	Neonates			Infants		
	S100B <P75th (*n* = 22)	S100B>P75th (*n* = 15)	*P* value	S100B <P75th (*n* = 32)	S100B>P75th (*n* = 23)	*P* value
Preoperative course						
ScO_2 (%)	65 ± 11	66 ± 7	.587	53 ± 12	59 ± 12	.069
SsO_2 (%)	63 ± 9	66 ± 6	.297	66 ± 10	66 ± 10	.901
$\Delta SacO_2$ (%)	25 ± 10	26 ± 8	.645	28 ± 11	35 ± 11	**.018**
AUC40 ScO_2 (min%)	0 (0-0)	0 (0-0)	.410	0 (0-42)	51 (0-550)	.151
SaO_2 (%)	89 ± 5	91 ± 4	.249	87 ± 10	88 ± 10	.825
MAP (mm Hg)	48 ± 4	50 ± 3	.074	na	na	na
pCO_2 (mm Hg)	44 ± 10	43 ± 6	.795	na	na	na
pO_2 (mm Hg)	58 ± 27	51 ± 14	**.042**	na	na	na
Intraoperative data						
ScO_2 (%)	72 ± 10	76 ± 7	.234	62 ± 10	57 ± 12	.156
SsO_2 (%)	77 ± 11	80 ± 8	.313	84 ± 9	83 ± 7	.618
AUC40 ScO_2 (min%)	0 (0-1)	0 (0-0)	.504	8 (0-123)	29 (0-279)	.338
Early postoperative course (first 4 hours)						
ScO_2 (%)	59 ± 14	57 ± 15	.648	63 ± 12	54 ± 13	**.011**
SsO_2 (%)	83 ± 15	88 ± 8	.168	87 ± 8	82 ± 10	**.049**
$\Delta SacO_2$ (%)	33 ± 12	34 ± 11	.780	30 ± 10	38 ± 11	**.008**
SaO_2 (%)	91 ± 8	92 ± 7	.929	92 ± 9	91 ± 11	.588
MAP (mm Hg)	53 ± 6	54 ± 6	.775	72 ± 10	10 ± 7	.269
pCO_2 (mm Hg)	39 ± 6	37 ± 7	.601	44 ± 7	45 ± 7	.850
pO_2 (mm Hg)	95 ± 56	95 ± 54	.993	108 ± 58	94 ± 55	.362
SvO_2 (%)	71 ± 12	73 ± 8	.509	61 ± 9	56 ± 13	.129
Lactate (mmol/l)	5.4 ± 1.9	7.4 ± 2.1	**.005**	1.7 ± 0.7	2.3 ± 0.9	**.006**
Entire postoperative course						
ScO_2 (%)	72 ± 10	71 ± 13	.816	67 ± 9	62 ± 8	**.047**
SsO_2 (%)	78 ± 11	77 ± 12	.894	77 ± 8	73 ± 9	**.044**
$\Delta SacO_2$ (%)	20 ± 7	21 ± 9	.661	24 ± 6	28 ± 7	.063
AUC40 ScO_2 (min%)	6 (0-69)	0 (0-177)	.593	2 (0-42)	47 (0-641)	.046
SaO_2 (%)	91 ± 8	91 ± 7	.932	92 ± 9	89 ± 10	.381
MAP (mm Hg)	50 ± 4	49 ± 3	.492	64 ± 5	49 ± 6	.451
pCO_2 (mm Hg)	43 ± 2	44 ± 4	.380	45 ± 5	46 ± 5	.789
pO_2 (mm Hg)	86 ± 40	87 ± 50	.930	92 ± 41	79 ± 39	.254
SvO_2 (%)	73 ± 8	72 ± 9	.862	65 ± 7	59 ± 9	**.021**
Max. lactate (mmol/l)	6.6 ± 2.0	8.1 ± 2.1	**.039**	2.3 ± 0.9	3.4 ± 1.4	**.003**

Bold values indicates statistical significance.

Abbreviations: AUC40 ScO_2, area under the curve below ScO_2 threshold of 40%; MAP, mean arterial pressure; $paCO_2$, arterial carbon dioxide tension; paO_2, arterial oxygen tension; SaO_2, arterial oxygen saturation; ScO_2, cerebral tissue oxygen saturation; SsO_2, somatic tissue oxygen saturation; $\Delta SacO_2$, arterial-cerebral saturation difference; SvO_2, central venous saturation.

baseline values within the first 24-72 hours.[22,23,27-29] Contamination by extracerebral sources needs to be considered as a potential confounder, but experimental data also suggest that early astrocyte activation after reperfusion is an important source of S100B release into the blood stream.[30-34] In children undergoing surgery for CHD without CPB, postoperative S100B was not increased as compared to preoperative values, while a significant increase was seen in patients operated with CPB.[35] In our cohort there was a correlation between the duration of CPB and S100B levels immediately after surgery in infants, but surprisingly not in the group of neonates. S100B levels in previous studies were also correlated with circulatory arrest times and to the duration of CPB, which suggests a direct impact of

extracorporeal circulation on astrocyte function.[27,36] CPB probably initiates a marked, but transient release of S100B into the systemic circulation, which is not necessarily associated with neuronal injury.

In contrast, a prolonged decrease or a delayed rises of S100B may reflect preceding or ongoing astrocyte injury. A pronounced secondary rise of S100B levels after surgery has been associated with adverse neurologic outcome.[23,37,38] In addition to acute neurological outcome, postoperative S100B levels 48 hours after surgery were identified as a risk factor for impaired neurodevelopment in infants undergoing surgery for CHD before 2 months of age.[24] For our study, we also identified patients with elevated S100B values after 24 or 48 hours. Clinical overt neurological injury was not noted in any patient within the first 48 postoperative hours. Consistent with this finding, absolute S100B values were only mildly elevated in comparison to normal values.[25,26] The relationship between S100B levels and neurodevelopmental outcome still needs to be determined. Outcome parameters, such as duration of mechanical ventilation or inotropic support and frequency of postoperative complications were not associated with elevated S100B concentrations in neonates. In contrast, a higher frequency of postoperative adverse events and an increased length of inotropic support was noted in infants with elevated S100B.

4.3 | Cerebral oxygenation and S100B

Near infrared spectroscopy allows noninvasive and real-time measurement of cerebral and somatic tissue oxygen saturation. It seems to be intuitively evident that hypoxic injury will occur below certain tissue oxygen saturations. Experimental data suggest that significant cerebral desoxygenation is likely to impact negatively on cerebral function.[39,40] A clinically validated lower threshold or a critical duration of decreased cerebral NIRS values has not been defined. Values between 40% and 45% are often used as lower thresholds in the clinical setting.

Decreasing cerebral tissue oxygen saturations are frequently observed in the early postoperative course, especially in neonates with complex CHD undergoing surgery with hypothermic CPB.[41-44] Our hypothesis, that postoperative S100B levels are related to perioperative cerebral oxygenation assessed by NIRS could not be proven in neonates. However, in the group of infants, we could demonstrate a relationship between elevated postoperative S100B concentrations and impaired postoperative cerebral oxygenation, either in terms of lower ScO_2 values or higher cerebral oxygen extraction estimated by a wider arterial-cerebral saturation difference. Lower postoperative cerebral tissue oxygen saturations have been associated with worse developmental outcome and cognitive abilities or structural cerebral changes in MRI.[14,15,17-19] In addition to postoperative cerebral tissue oxygen saturation, preoperative cerebral oxygenation in terms of a wider arterial-cerebral oxygen saturation difference was also related to S100B elevations in the later postoperative course. It is possible that altered preoperative cerebral oxygenation influences the susceptibility to cardiopulmonary bypass and subsequent release of S100B.

NIRS often serves as a monitoring for adequacy of cerebral tissue oxygenation during CPB. ScO_2 on CPB is influenced by flow-rate, temperature and hematocrit. During deep hypothermic bypass relatively high values of ScO_2 are usually achieved even with low flow rates, while higher flow rates are required to obtain similar ScO_2 values at higher temperature. Lower ScO_2 thresholds associated with functional or histologic brain injury have been evaluated in animal experiments but such thresholds have not been determined for children undergoing cardiac surgery.[45] In our study, mean ScO_2 values for the entire intraoperative period were not different between cases with elevated postoperative S100B or concentrations in the normal range. But ScO_2 tended to be lower while on CPB from cooling until rewarming in infants and was significantly lower in the subgroup of noncyanotic infants or patients with abolished cyanosis after corrective surgery. A wide cerebral arterio-venous saturation difference during cardiopulmonary bypass or the decrease of cerebral saturations during reperfusion measured by near-infrared spectroscopy was associated with increased serum S100B in the perioperative period in a previous study.[29] In addition, brain MRI abnormalities in terms of hemosiderin foci were associated with lower average ScO_2 in infants undergoing corrective surgery for CHD.[15] Average ScO_2 were also above widely accepted thresholds for patients with or without imaging abnormalities.[15] NIRS thresholds for adequate cerebral oxygenation may vary according to underlying CHD and specific bypass conditions. Further studies are needed to determine whether NIRS-guided CPB management can improve neurodevelopmental outcome.

4.4 | Association between S100B and routine monitoring data

In both, neonates and infants, a relation between elevated S100B concentrations in the later postoperative course and lactate levels existed. In both groups, there was a correlation between initial lactate levels and S100 values 24 hours after surgery. The primary source of postoperative hyperlactatemia after CPB is not necessarily the brain, but it represents a global intraoperative or early postoperative tissue oxygen debt, impaired lactate clearance, or both. Postoperative lactate levels and derived variables have been described as an early outcome predictor, particularly of survival but also for developmental outcome in children with CHD undergoing repair or palliation with cardiopulmonary bypass.[24,46,47]

5 | LIMITATIONS

The clinical utility of S100B as a brain biomarker has been questioned by evidence of extracerebral sources, including adipose tissue.[30-33] The avoidance of direct postoperative samples to identify patients at risk, may minimize possible contamination from extracerebral sources due to surgical trauma. Data regarding reliable normal values for healthy children is sparse and the use of different assays limits comparability. To allow statistical comparisons, the 75th percentile was used

to define elevated S100B concentrations in this study. However, this threshold may be too low to define pathological S100B elevations. The relatively wide range of S100B serum concentrations in healthy newborns limits the use of S100B as a reliable biomarker in this age group and might also explain the missing correlation between S100B concentrations and NIRS data or variables related to surgery.[25,26]

Cerebral MRI was not performed in the perioperative course and no association between S100B values or cerebral tissue oxygenation and evidence of brain injury can be provided. In this observational study NIRS monitoring was not used for a goal-directed therapy. No protocols for interventions if NIRS values were below certain thresholds existed. A larger group of patients is needed, especially for subgroup analysis.

6 | CONCLUSIONS

Our study demonstrates a relationship between elevated postoperative S100B concentrations and altered cerebral oxygenation in term of lower cerebral tissue oxygen saturations and higher oxygen extraction after cardiac surgery utilizing cardiopulmonary bypass in infants beyond the neonatal period. The astrocyte protein S100B might serve as a surrogate parameter for cerebral hypoxemia after surgery for CHD. The relationship between S100B levels and neurodevelopmental outcome still needs to be determined.

CONFLICT OF INTEREST STATEMENT

All Authors have nothing to disclose with regard to commercial support.

AUTHOR CONTRIBUTIONS

All listed authors fulfilled authorship criteria: (1) substantial contributions to research design, or the acquisition, analysis, or interpretation of data; (2) drafting the article or revising it critically; and (3) approval of the submitted and final versions.

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