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Age difference of the relationship between cerebral oxygen saturation and physiological parameters in pediatric cardiac surgery with cardiopulmonary bypass — analysis using the random-effects model

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Abstract

Recently, monitoring of cerebral oxygen saturation (ScO₂) has become widespread in pediatric cardiac surgery. Our previous study reported that mean blood pressure (mBP) was the major contributor to ScO₂ throughout cardiac surgery with cardiopulmonary bypass (CPB) in children weighing under 10kg. We speculated that this result might be attributable to incomplete cerebral autoregulation in such young children. Accordingly, our hypothesis is that the relationship between ScO₂ and the physiological parameters may change according to the growth of the children.

ScO₂ was measured with an INVOS 5100C (Somanetics, Troy, MI). Random-effects analysis was employed with ScO₂ as a dependent variable, and seven physiological parameters (mBP, central venous pressure, nasopharyngeal temperature, SaO₂, hematocrit, PaCO₂, and pH) were entered as independent covariates. The analysis was performed during the pre-CPB, CPB and post-CPB periods by dividing the patients into two groups: infants (Infant Group) and children who were more than 1 year old (Child Group).

The Infant and Child Groups consisted of 28 and 21 patients. In the random-effects analysis, mBP was the major contributor to ScO₂ during CPB in both groups. During the

pre-CPB period, the effect of mBP was strongest in the Infant group. However, its effect was second to that of SaO₂ in the Child Group. During the post-CPB period, SaO₂ and mBP still affected ScO₂ in the Infant group. However, the dominant contributors were unclear in the Child Group.

Cerebral autoregulation may be immature in infants. In addition, it may be impaired during CPB even after one year of age.

Key Words: cerebral oxygen saturation; pediatric cardiac surgery; cardiopulmonary bypass; random-effects model; cerebral autoregulation; age

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Introduction

Recently, monitoring of cerebral oxygen saturation (ScO₂) has become widespread in pediatric cardiac surgery because neuronal injury is not necessarily rare even now [1,2]. However, the value of the monitoring seems not to be well established, including that regarding the effectiveness of intraoperative use[3,4]. We hypothesized that one of the reasons why its value is not well established may be that the physiological factors affecting ScO₂ in the perioperative period of pediatric cardiac surgery have not been sufficiently clarified. Accordingly, we performed a study to observe the changes in ScO₂ during cardiac surgery with cardiopulmonary bypass (CPB) in children weighing under 10kg and evaluated the relationship with the physiological parameters by using a random-effects model [5]. We found that systemic blood pressure was the major contributor to ScO₂ throughout the cardiac surgery with CPB in these children. This tendency was seen regardless of the type of congenital heart disease, i.e., the univentricluar or biventricular physiological type. We speculated that this result might be attributable to incomplete cerebral autoregulation in such young children [6]. If so, the relationship between ScO₂ and the physiological parameters may change according to the growth of the children.

Accordingly, in this study, we observed the changes in ScO₂ during cardiac surgery with CPB in children over a wider age range and evaluated the relationship with the physiological parameters by using the random-effects model. For this analysis we divided the children into 2 age groups: infants (0 years old) and children (more than 1 year old).

Patients and Methods

This prospective observational study was approved by Institutional Review Board of the Hokkaido University Hospital (IRB #016-0505) and written informed consent was obtained from the parents of all subjects participating in the trial. The trial was registered at UMIN Clinical Trials Registry prior to patient enrollment (UMIN000028597).

Children who were under 15 years old and who were scheduled for cardiac surgery with CPB were examined. Children with complications of other organs were excluded. Anesthesia and perioperative management, including ICU care, were conducted according to our institutional practices [5,7]. In brief, fentanyl (15-25µg/kg) and remifentanil (0.1-0.5µg/kg/min) were supplemented with midazolam (0.2-0.5mg/kg) and sevoflurane (1-2%) as tolerated, and neuromuscular blockade was achieved with rocuronium. Standard monitoring was used, including a femoral artery catheter for measurement of systemic arterial blood pressure and intermittent blood sampling and an internal jugular catheter for measurement of central venous pressure (CVP). In the cardiopulmonary bypass, a nonpulsatile roller pump with a membrane oxygenator (Oxia, JMS, Tokyo, Japan) was used at a flow rate of 150 ml/min/kg. The alpha-stat strategy was used during core cooling.

ScO₂ was measured with an INVOS 5100C (Somanetics, Troy, MI, USA). After induction of anesthesia, SomaSensors® (Somanetics, Troy, MI, USA) were placed on the right side of the forehead. A pediatric sensor (CV-SPFB/INTL) was used for the children whose body weight was from 5 to 40kg and an infant sensor (CV-CNN/SNN) was used for the children who weighed less than 5kg. After an accommodation period, data collection was begun every one minute throughout the surgery. Mean arterial pressure (mBP), CVP, and nasopharyngeal temperature (Tnp) were also obtained every one minute. Arterial blood gases were analyzed at 37°C intermittently and the arterial oxygen saturation (SaO₂), PaCO₂, pH and hematocrit (Hct) were obtained. These measurements were linearly interpolated to one-minute intervals.

Statistics

JMP 14 (SAS, Cary, NC, USA) was used for statistical analysis. The main purpose of this study was to examine the relation between the changes of ScO₂ values and physiological parameters according to the growth of children. For this, random-effects analysis was employed for ScO₂ as a dependent variable. In each analysis, seven physiological parameters (mBP, CVP, Trectal, SaO₂, Hct, PaCO₂, and pH) were entered as independent covariates. The analysis was done for each infant (Infant Group) and for children who were more than 1 year old (Child Group). It was performed during the pre-

CPB period (from the start of operation to the start of CPB), CPB period and post-CPB period (from the end of CPB to the end of surgery) in each group. The mean regression slope, its confidence interval and p-values were obtained for each parameter. P-values were displayed as negative log₁₀ values because they were so small.

Results

Forty-nine patients were evaluated. The Infant and Child Groups consisted of 28 and 21 patients, respectively. Demographic data are listed in Table 1. During CPB, mild hypothermia and normothermia were used in 18 patients of the Infant Group and 13 patients of the Child Group. In the Infant Group, 7 patients had congenital heart disease with univentricular physiology (PA, HLHS, univentricular heart). Six patients had congenital heart disease with univentricular physiology in the Child Group. Physiological data during pre-CPB, CPB and post-CPB are listed in Table 2. Throughout the whole surgical period, ScO₂ values in the Child Group were higher than those in the Infant Group, although we did not perform statistical analysis of ScO₂ values as we did with other physiological parameters because the comparison of the absolute values was not the purpose of this study.

The results of random-effects analysis for ScO₂ in the Infant Group are listed in Table 3. For the analysis of the pre-CPB period in the Infant Group, 1,2782 data (1,826 1-min records of 7 parameters) were entered. For the analyses of the CPB and post-CPB periods, 27,776 data (3,968 1-min records of 7 parameters) and 12,761 data (1,823 1-min records of 7 parameters) were entered, respectively. During the Pre-CPB and CPB periods, ScO₂

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was correlated strongly with mBP. SaO₂ was secondarily related to ScO₂ in the same periods. During the post-CPB period, their order was reversed.

The results of random-effects analysis for ScO₂ in the Child Group are listed in Table 4. For the analysis of the pre-CPB period, 11,620 data (1,660 1-min records of 7 parameters) were entered. For the analyses of the CPB and post-CPB periods, 19,964 data (2,852 1-min records of 7 parameters) and 9,884 data (1,412 1-min records of 7 parameters) were entered, respectively. During the CPB period, ScO₂ was correlated strongly with mBP as in the Infant group. On the other hand, the contribution of mBP was second to that of SaO₂ during the pre-CPB period. The dominant contributors were unclear during the post-CPB period.

Representative cases of simultaneous changes of ScO₂ and mBP over time are shown in Figure 1. The changes in ScO₂ and mBP were almost parallel during the CPB period in a 3-month-old female with AVSD (Fig 1A). On the other hand, ScO₂ and mBP sometimes changed to the opposite direction in a 5-year-old male with VSD during the post-CPB period (Fig 1B).

Discussion

Our study revealed that mBP was the major contributor to ScO₂ during the CPB period in pediatric cardiac surgery with CPB, regardless of any age difference. On the other hand, the contribution of mBP became weak during the pre-CPB and post-CPB periods after one year of age.

During the pre-CPB period, the contribution of mBP was strong in the infant group. However, it became weak after one year of age. Recent findings suggest that term infants have functional autoregulation and vasoreactivity, whereas preterm infants may have anatomically incomplete and underdeveloped cerebral vasculature that cannot yet autoregulate fully[8]. Another study also indicated that static cerebral autoregulation was preserved in infants and children under sevoflurane anesthesia [9]. On the other hand, a recent study reported that term newborns with congenital heart disease showed impaired cerebral autoregulation [10]. Indeed, it was reported that term newborns with congenital heart disease have brains that are smaller and structurally less mature than expected before they undergo cardiac surgery [11,12]. Accordingly, cerebral autoregulation of infants with congenital heart disease may still be immature.

As to the CPB period, mBP was the major contributor to ScO2 even in the children

more than 1 year old. One study examined the relationships of ScO₂ with physiological parameters in 20 infants with the biventricular physiological type [13]. In that study, ScO₂ showed significant positive correlations with mBP. In another study, the relationship of ScO₂ with physiological parameters during CPB was evaluated in 10 children from 12 days to 9 years old [14]. ScO₂ correlated positively with cerebral perfusion pressure (mBP-CVP) and the partial variance was more than 50%. Accordingly, those previous reports also suggested that the changes in ScO₂ were dependent on mBP changes during CPB. It is well known that cerebral blood flow (CBF) is one of the important determinants of ScO₂ [7]. Accordingly, it is suggested that the changes in CBF were dependent on mBP changes during CPB, possibly due to immature or disturbed cerebral autoregulation.

Cerebral autoregulation during CPB in pediatric cardiac surgery has been evaluated for a long time. One old study evaluated the relationship between mBP and CBF measured by xenon-clearance technique in 67 pediatric patients, aged 1 day–16 years [15]. During moderate-hypothermic CPB (25–32°C), there was no association between CBF and mBP. However, during deep-hypothermic CPB (18–22°C), there was an association between them. Another paper evaluated the relationship between mBP and CBF velocity measured by transcranial Doppler monitor in 25 neonates and infants, aged 3–210 days [16]. A thirdorder polynomial function showed that cerebral pressure-flow velocity autoregulation was intact during normothermic CPB (36–37°C). However, cerebral pressure-flow velocity autoregulation became pressure-passive during deep-hypothermic CPB (23–25°C) and profound-hypothermic CPB (14–20°C). These old studies suggested that static cerebral autoregulation was preserved during CPB except under deep hypothermia.

Recently, several studies evaluated dynamic cerebral autoregulation during cardiac operations, including pediatric ones [17,18]. In one study of 54 children undergoing cardiac surgery with CPB, the cerebral oximetry index was calculated as a moving, linear correlation coefficient between slow waves of arterial blood pressure and cerebral oximetry measured with near-infrared spectroscopy [17]. Their mean age was 56 months old and the mean minimum temperature during CPB was 26.9°C. The mean cerebral oximetry index increased during CPB compared to pre-CPB, which indicated impaired cerebral autoregulation. In another study which utilized almost the same methodology, dynamic cerebral autoregulation was impaired during CPB under moderate hypothermia at around 28°C in children whose median age was 2.8 years [18]. On the other hand, there seem to be no data about dynamic cerebral autoregulation under mild hypothermia or normothermia, which our institute mainly adopts. However, in 234 adult patients undergoing coronary artery bypass graft surgery, valvular surgery, or both that required CPB under mild hypothermia at around 35°C, 20% of patients demonstrated impaired dynamic cerebral autoregulation during CPB using almost the same methodology as described above [19]. Thus, there is possibility that cerebral autoregulation is impaired during CPB under mild hypothermia even in adult patients. Accordingly, cerebral autoregulation may be impaired during CPB under mild hypothermia or normothermia in pediatric cardiac surgery.

During the post-CPB period, the contribution of mBP became weak even in the infants. Moreover, the dominant contributors were unclear in the children. In our previous study, the contribution of mBP also became weak compared to the pre-CPB and CPB periods in patients whose body weight was less than 10kg [5]. On the other hand, it is hard to think that immature cerebral autoregulation became mature after CPB in the infants. During the post-CPB period, cardiovascular agents that affect cerebral blood flow [20] are usually used. In addition, the degree of surgical repair may affect cardiac and respiratory functioning after CPB. Accordingly, such extrinsic factors other than physiological ones may make interpretation difficult.

Throughout the whole surgical period, ScO_2 values in the Child Group were higher than those in the Infant Group, although we did not statistically analyze this. This finding is compatible with recent reports. In one study, ScO_2 values before surgery showed a statistically significant increasing relationship with age in children with VSD younger than 3 years [21]. In another study, ScO_2 values before and after surgery increased simultaneously with the increase in age between 0 and 7 years in children with noncyanotic congenital heart disease [22]. If the absolute values are different according to the growth of children, the threshold values of ScO_2 may be different with the difference of age. It is clinically important to clarify the threshold values. The mechanism of the difference of ScO_2 values according to the growth of children should be evaluated as the next step as well the setting of the threshold values by the difference of age.

There are some limitations in our study. First, there were fewer than 10 patients with the univentricular physiological type in each group. Therefore, we could not analyze by dividing the patients into univentricular and biventricular physiological types. However, in our previous study, the tendency was the same for the univentricular and biventricular physiological types, at least in patients weighing under 10kg [5]. Second, 20 of the 21 patients were under 6 years old in the Child Group. Therefore, we could not evaluate school children. Third, as mentioned above, more than half of the patients were managed under mild hypothermia or normothemia during CPB in both groups. When the population managed by moderate or deep hypothermia increases, the effect of body temperature and/or mBP on ScO₂ might be more complicated [23]. Fourth, there are some measurement algorithms utilized in near infrared spectroscopy including the modified Beer Lambert law (which the INVOS 5100C utilizes), spatially resolved spectroscopy and time-resolved spectroscopy. It was reported that absolute ScO₂ values were different among the different spectroscopic techniques in both adults [24] and infants [25] studies. Moreover, by using a spectroscopic technique that adopts time-resolved spectroscopy, further information such as the absolute values of oxy- and deoxy hemoglobin can be obtained [26]. Thus, it may be necessary to reexamine the findings by using other spectroscopic techniques. Fifth, in this study, we evaluated the relation between ScO₂ and physiological parameters, including mBP. However, to examine whether cerebral autoregulation really exists, continuous analysis of the direct relation between mBP and ScO₂ like the cerebral oximetry index will be necessary [17,18].

In conclusion, mBP was the major contributor to ScO₂ during the CPB period regardless of age in pediatric cardiac surgery. In addition, cerebral autoregulation may be immature in infants. Accordingly, the management of blood pressure in this situation is important in pediatric cardiac surgery.

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Figure legend

Figure 1 Representative cases of simultaneous changes of ScO₂ and mBP over time

- (A) during the CPB period in a 3-month-old female with AVSD
- (B) during the post-CPB period in a 5-year-old male with VSD

Circles indicate changes in ScO₂ and squares indicate changes in mBP. Time indicates minutes after the start of CPB (A) and after the end of CPB (B).

Table 1 Demographic data of the patients

	Infants Group	Children Group
Male/female	14/14	15/6
Age	118 (85-165) days	30 (24-46) months
Body weight (kg)	4.5 (2.5-8.4)	12 (8.1-22.5)
Surgical time (min)	254 (101-369)	211 (132-511)
CPB time (min)	176 (52-243)	158 (41-329)
Management of body temperatu	re during CPB	
Normothermia (<35°C)	7	10
Mild hypothermia (32-34.9°C)	11	3
Moderate hypothermia (28-31.	9°C) 6	5
Deep hypothermia (27.9°C)	4	3
Diagnosis		
ASD	0	4
VSD	2	0
VSD with ASD	3	1
AVSD	5	0
TOF	4	4
TGA	2	2
DOLV	1	2
PA	1	1
HLHS	5	3
Univentricular Heart	1	2
Others	4	2

Data are expressed as medians (interquartile range).

ASD; atrial septal defect, VSD; ventricular septal defect, AVSD; atrioventricular septal defect, TOF; tetralogy of Fallot, TGA; transposition of the great arteries, DOLV; double outlet right ventricle, PA; pulmonary atresia, HLHS; hypoplastic left heart syndrome

	Pre-CPB	CPB	post-CPB	
ScO ₂ (%)				
Infants Group	56.7 ± 16.2	61.8 ± 14.8	61.2 ± 18.0	
Children Group	76.0 ± 11.7	70.2 ± 10.5	80.5 ± 9.7	
mBP (mmHg)				
Infants Group	45.3 ± 8.6	44.9 ± 12.6	56.2 ± 10.7	
Children Group	53.0 ± 9.2	39.7 ± 12.6	51.7 ± 8.9	
CVP (mmHg)				
Infants Group	7.9 ± 3.4	5.6 ± 6.3	13.1 ± 5.3	
Children Group	9.7 ± 3.5	6.0 ± 5.6	12.3 ± 4.5	
Tnp (°C)				
Infants Group	37.2 ± 1.1	34.1 ± 2.4	36.3 ± 1.0	
Children Group	37.5 ± 0.8	34.2 ± 2.9	36.6 ± 1.1	
SaO ₂ (%)				
Infants Group	88.5 ± 8.3	98.6 ± 3.5	90.1 ± 9.6	
Children Group	90.5 ± 7.5	98.7 ± 2.9	97.8± 3.0	
рН				
Infants Group	7.35 ± 0.05	7.31 ± 0.06	7.31 ± 0.05	
Children Group	7.35 ± 0.04	7.29 ± 0.06	7.30 ± 0.06	
PCO ₂ (mmHg)				
Infants Group	44 ± 8	45 ± 8	43 ± 7	
Children Group	38± 4	43 ± 8	42 ± 5	
Hct (%)				
Infants Group	$38.6{\scriptstyle\pm}6.4$	36.1 ± 5.4	41.7 ± 4.9	
Children Group	38.4 ± 5.2	33.0 ± 5.3	37.4 ± 6.5	

Table 2 Physiological data during pre-CPB, CPB and post-CPB periods

ScO₂, mBP, CVP and Trnp values obtained every one minute were averaged during each

term. SaO₂, PaCO₂, pH and Hct values, which were obtained intermittently and linearly interpolated to minute intervals, were averaged during each term. The data are expressed as mean \pm standard deviation.

pre-CPB		
Parameters	Random-effects model for ScO_2 (pre CPB period)	
	Mean regression slope (95% Cl)	-log ₁₀ (p value)
mBP	0.48 (0.44, 0.52)	115.2
SaO ₂	0.35 (0.26, 0.43)	14.6
CVP	-0.50 (-0.62, -0.37)	13.7
рН	90.8 (50.5, 131.0)	5.0
PaCO ₂	0.56 (0.21, 0.92)	2.8
Tnp	1.41 (0.49, 2.32)	2.6
Hct	0.55 (0.04, 1.06)	1.4

Table 3 Relations of ScO_2 with physiological parameters in the Infant Group

СРВ

Parameters	Random-effects model for ScO ₂ (CPB period)		
	Mean regression slope (95% CI)	$-\log_{10}$ (p value)	
mBP	0.26 (0.24, 0.29)	103.8	
SaO ₂	0.61 (0.54, 0.68)	64.2	
PaCO ₂	0.54 (0.47, 0.62)	44.9	
рН	66.1 (56.6, 75.5)	41.2	
Hct	0.38 (0.30, 0.45)	21.8	
Tnp	-0.26(-0.38, -0.13)	4.1	
CVP	-0.03 (-0.09 to 0.02)	0.6	

post-CPB

Parameters	Random-effects model for ScO ₂ (post CPB period)		
	Mean regression slope (95% Cl)	-log ₁₀ (p value)	
SaO ₂	0.34 (0.25, 0.43)	12.4	
mBP	0.10 (0.07, 0.13)	8.9	
Hct	-0.21 (-0.29, -0.14)	7.3	
рН	-26.7 (-39.4, -14.0)	4.4	
Tnp	1.04 (0.51, 1.56)	4.0	
CVP	0.14(0.05, 0.23)	2.8	
PaCO ₂	-0.02 (-0.11, 0.06)	0.2	

pre-CPB			
Parameters	Random-effects model for ScO ₂ (pre CPB period)		
	Mean regression slope (95% Cl)	-log ₁₀ (p value)	
SaO ₂	0.92 (0.79, 1.04)	41.6	
mBP	0.20 (0.16, 0.24)	23.6	
CVP	-0.34 (-0.44, -0.23)	9.3	
рН	47.7 (26.5, 68.8)	5.0	
Tnp	-0.90(-1.71, -0.09)	1.5	
Hct	-0.25 (-0.63, 0.13)	0.7	
PaCO ₂	0.55 (0.04, 1.06)	0.1	

Table 4 Relations of ScO_2 with physiological parameters in the Children Group

СРВ

Parameters	Random-effects model for ScO ₂ (CPB period)		
	Mean regression slope (95% Cl)	-log ₁₀ (p value)	
mBP	0.37 (0.33, 0.41)	68.4	
CVP	0.53 (0.43, 0.62)	27.6	
SaO ₂	0.49 (0.39, 0.59)	22.0	
Hct	0.25 (0.17,0.34)	9.0	
Tnp	0.42 (0.26, 0.59)	6.3	
рН	-17.7(-30.4,-5.1)	2.2	
PaCO ₂	-0.09 (-0.20, 0.01)	1.1	

post-CPB

Parameters	Random-effects model for ScO ₂ (post CPB period)	
	Mean regression slope (95% Cl)	-log ₁₀ (p value)
Tnp	-0.76 (-1.19, -0.34)	3.4
CVP	0.20 (0.09, 032)	3.4
рН	-23.0 (-35.8, -10.3)	3.4
PaCO ₂	0.16 (0.03, 0.28)	1.8
SaO ₂	-0.19 (-0.40, 0.02)	1.1
Hct	-0.10 (-0.21, 0.02)	1.0
mBP	-0.01 (-001, 0.04)	0.2



mBP (mmHg)

Time (min)



mBP (mmHg)

Time (min)