의학석사 학위논문

Impact of hemodilution on variability of cerebral oxygen saturation during cardiopulmonary bypass in children with cyanotic congenital heart disease

청색증형 선천성 심장병 소아 환자에서
심폐우회로 동안 혈액 희석이
뇌산소포화도 변동성에 미치는 영향

울 산 대 학 교 대 학 원
의 학 과
서 미 숙

Impact of hemodilution on variability of cerebral oxygen saturation during cardiopulmonary bypass in children with cyanotic congenital heart disease

지 도 교 수　　신 원 정

이 논문을 의학석사 학위 논문으로 제출함

2018년 12월

울 산 대 학 교　대 학 원
의　학　과
서 미 숙

서미숙의 의학석사학위 논문을 인준함

심사위원 최우종 (인)

심사위원 신원정 (인)

심사위원 송인경 (인)

울 산 대 학 교 대 학 원

2018년 12월

Abstract

Background Children with cyanotic congenital heart disease (CHD) who are exposed to chronic hypoxemia compensate by increasing the hematocrit concentration to maintain adequate cerebral oxygenation. However, the rapid decrease in hematocrit due to cardiopulmonary bypass (CPB) administration in these patients may have a negative impact on cerebral oxygenation. The aim of this study was to investigate cerebral oxygen variability in the course of CPB in children with CHD undergoing cardiac surgery, using performance measurement of cerebral oxygen saturation ($rScO_2$) and assessing whether the values are related to changes in hematocrit.

Methods 93 children (acyanotic CHD 48, cyanotic CHD 45) who had undergone cardiac surgery using CPB with $rScO_2$ monitoring were enrolled. Median performance error (MDPE), median absolute performance error (MDAPE), and wobble parameters of performance measurement were calculated with $rScO_2$ for each interval by dividing the data into pre-CPB, during-CPB and post-CPB stages. The $rScO_2$ level before the induction of anesthesia was used as a reference value. The correlation between the parameters of performance measurement and the decrease in hematocrit (ΔHct = baseline hematocrit – hematocrit of each CPB stage) was also examined.

Results Pre-CPB $rScO_2$ was similar (67% vs. 66%) in the cyanotic group, however, MDPE was significantly lower (0% vs. -2.9%, P=0.027) and wobble was larger (6.7% vs. 10.1%,

P=0.041) compare with the acyanotic group. In the during-CPB stage, MDPE, MDAPE, and wobble were not significantly different between acyanotic and cyanotic CHD. In cyanotic CHD children, MDPE (P=0.032) and MDAPE (P=0.024) were significantly correlated with ΔHct in the during-CPB stage, whereas was not in acyanotic CHD. In the post-CPB stage, cyanotic patients had lower $rScO_2$ (59.2% vs. 54.9%, P=0.032) and MDPE (-10.5% vs. -18.5%, P=0.002), and higher MDAPE (19.5% vs. 14%, P=0.005) than the acyanotic group.

Conclusion Baseline $rScO_2$ of children with cyanotic CHD is maintained in the normal range through compensatory mechanisms including hemoconcentration, although variability was greater than for acyanotic children. However, $rScO_2$ variabilities are correlated with the degree of hemodilution in the during-CPB stage in the cyanotic CHD group. Therefore, it should be noted excessive hemodilution may influence cerebral oxygenation during CPB in children with cyanotic CHD.

Keywords cerebral oxygen saturation, congenital heart disease, cardiopulmonary bypass

Table of contents

Tables and figures

Introduction

The postoperative survival rate of children with congenital heart disease (CHD) is increasing due to improved surgical techniques and cardiopulmonary bypass (CPB) management, and their neurodevelopmental outcomes are thus becoming of greater significance. In these children, several factors contribute to delayed neural development, but one of the most important is whether cerebral blood perfusion and oxygen delivery are sufficient (1-3). Ultimately, maintaining the balance of brain oxygen demand and supply is crucial for brain development.

Some CHD patients may develop cyanosis, which can persist for long periods of time with chronic hypoxia before correction. A key mechanism to compensate for chronic hypoxia is raised hemoglobin concentration, which increases arterial oxygen content and maintains tissue oxygen delivery (4). For this reason, the hemoglobin level is higher in children with cyanotic congenital heart disease than it is in acyanotic patients.

The factors affecting cerebral oxygen saturation ($rScO_2$) during CPB include loss of pulsation, target hypothermia, hemoglobin concentration, rapidness of rewarming, and blood pressure (5-8). Among these factors, acute hemodilution may have a negative impact on patients with cyanotic CHD who have maintained adequate $rScO_2$ by way of a high hematocrit compensating mechanism. In particular, $rScO_2$ could fluctuate significantly in the cooling phase of CPB, where the hematocrit decreases sharply, and the pulsatile flow disappears before

the hypothermic temperature is reached. The same effect could occur in the opposite situation, the rewarming phase.

The aim of this study was to determine whether the hematocrit change affected cerebral oxygenation variability in children with cyanotic CHD. To do this, we investigated $rScO_2$ fluctuations in each stage of CPB through performance measurement (PM) method.

Materials and methods

Patients and data collection

Electronic hospital databases and medical records of pediatric patients who had undergone cardiac surgery using CPB for congenital heart disease between Sep 2017 and Mar 2018 at Asan Medical Center (Seoul, Korea) were reviewed retrospectively. Inclusion criteria were that patients should be under five years old and diagnosed with atrial septal defect (ASD), ventricular septal defect (VSD), Tetralogy of Fallot (TOF), or functional single ventricle (FSV). ASD and VSD were classified as the acyanotic group, and TOF and FSV were classified as the cyanotic group. Patients with preexisting neurologic deficit, chromosomal anomaly, and total deep hypothermic circulatory arrest during operation were excluded. The data were analyzed by selecting 100 patients satisfying the above criteria.

Demographic data collected were age, gender, height, weight, and body surface area. Surgical data collected were preoperative peripheral oxygen saturation and total CPB duration. Anesthetic records were also collected and reviewed for arterial blood gas analysis (ABGA). ABGA results included pH, partial pressure of arterial oxygen (PaO_2), partial pressure of carbon dioxide tension ($PaCO_2$), arterial blood oxygen saturation (SaO_2), base excess, and hematocrit concentration.

Anesthesia and monitoring

All patients underwent general anesthesia according to Asan Medical Center's pediatric cardiac surgery protocol. Non-invasive blood pressure, electrocardiography, pulse oximetry, and capnography were applied. Cerebral oximetry based on near-infrared spectroscopy (NIRS, INVOS 5100, Somanetics, Troy, MI) was also monitored. The children were premedicated with midazolam 0.1mg/kg iv. Anesthesia was induced with midazolam 0.2-0.3mg/kg, fentanyl 3-5mcg/kg, and rocuronium 0.5mg/kg. Subsequently, drugs including midazolam, fentanyl, and rocuronium same as induction drugs were administered every 30 minutes to maintain anesthesia. After tracheal intubation, pressure-controlled ventilation was used, and the pressure was set to achieve a tidal volume of 7-8 ml/kg. Although the inspired oxygen concentration was set at 30%, it was adjusted up and down according to systemic or pulmonary blood flow changes. An arterial line was inserted into the radial artery or the femoral artery for repeated sampling and monitoring of arterial pressure. An ultrasound-guided central venous catheter (4-5.5 Fr; Arrow International Inc., Reading, PA) insertion was performed in the internal jugular vein. CPB began with aortic cannulation and bicaval venous drainage. The target flow of CPB was 2.4 L/min/m^2 and systemic cooling was performed. The patient's blood pH was maintained within a normal range throughout CPB. Modified ultrafiltration was applied immediately after CPB termination.

All intraoperative monitoring was recorded, including electrocardiography, arterial blood

pressure, central venous pressure, heart rate, body temperature, peripheral capillary oxygen saturation (SpO_2), and $rScO_2$ and was automatically stored every five seconds via Vital Recorder (9) throughout the entire operation. Recording started as soon as the patient entered the operating room. The anesthesiologist noted the beginning of CPB, the time points of body temperature change, and the end point of CPB. A total of five ABGA measurements were taken intraoperatively, after induction of anesthesia, during cooling after starting CPB, during hypothermic state, during rewarming, and finally, after CPB termination. In the ABGA results, gas partial pressures and hematocrit concentrations were obtained and were automatically registered in the hospital laboratory database.

$rScO_2$-derived parameters

PM of intraoperative $rScO_2$ was calculated using the formula proposed by Varvel et al. (10) in a study of drug concentration. The target concentration of the drug was set to the reference $rScO_2$ and the actual concentration to the measured $rScO_2$. The reference $rScO_2$ was the $rScO_2$ value measured before anesthesia, after the patient entered the operating room.

Based on pre-stored records, PM parameters of $rScO_2$ were automatically calculated using the R program in which the calculation formula was input. Calculations were based on dividing data between the pre-CPB stage, during-CPB stage, and post-CPB stage; the during-CPB stage was further divided into the cooling stage, cold (hypothermic) stage, and rewarming stage. We

used Varvel and colleagues' formula (10) for the bias and accuracy of the drug concentration in pharmacokinetic studies for PM calculation (Figure 1). Performance error (PE) is the difference between the target value and the actual value. The MDPE is the median of the PE values and indicates whether the actual value is higher or lower than the reference value. The MDAPE is the median of the absolute PE values. Wobble is the median of the absolute values of the MDPE and PE differences. After first calculating the PE of each point stored, the remaining parameters were also calculated. The formulas used to calculate PM parameters were as follows.

PE (%) = (measured $rScO_2$ – reference $rScO_2$) × 100 / reference $rScO_2$

MDPE (%) = median [PE_i, i= 1, 2, 3 …, N] (N, numbers of measured $rScO_2$)

MDAPE (%) = median [$|PE|_i$, i= 1, 2, 3 …, N] (N, numbers of measured $rScO_2$)

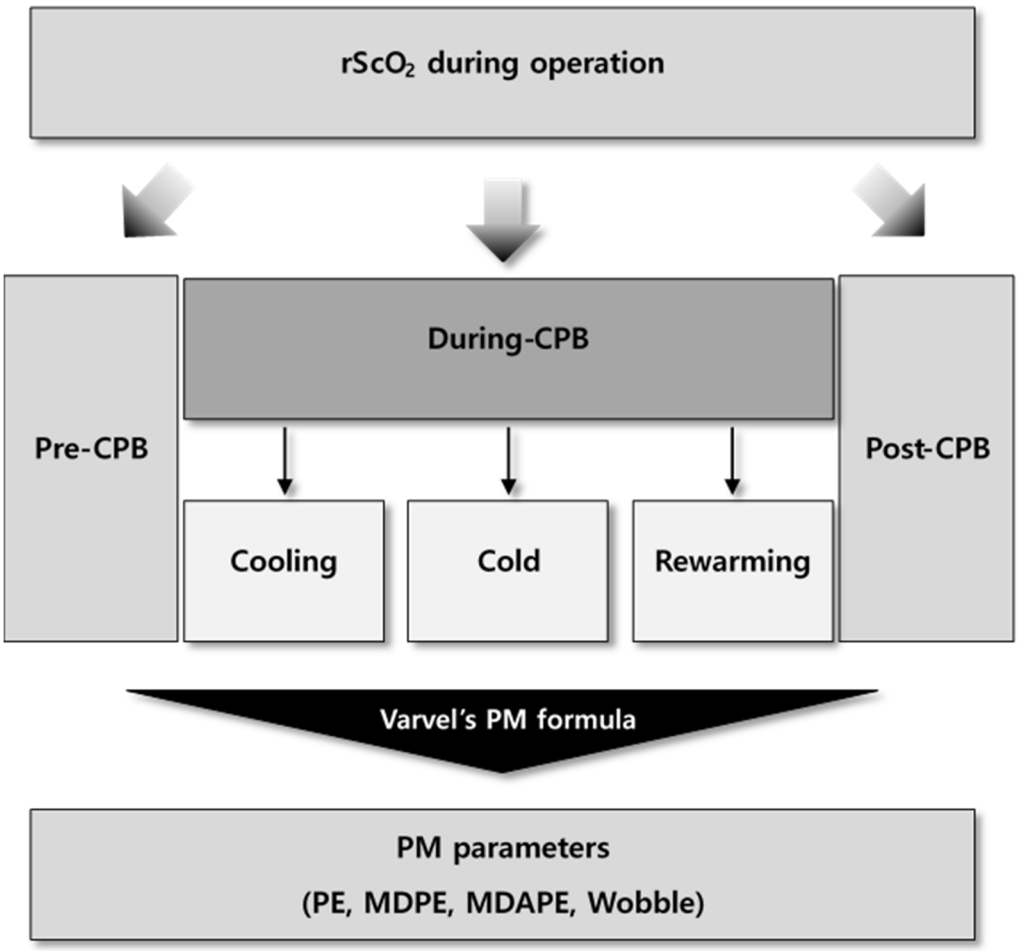
Wobble (%) = median [$|MDPE - PE_i|$, i= 1, 2, 3 …, N] (N, numbers of measured PE)

From the perspective of $rScO_2$, a positive MDPE value means a rise in $rScO_2$, and a negative MDPE value means a decrease in $rScO_2$. MDAPE represents the absolute value of the difference between the measured $rScO_2$ value and the reference value, but it does not indicate whether the level is ascending or descending. Wobble is the median absolute value of the MDPE minus PE; the larger this value, the more unstable becomes the $rScO_2$.

To analyze the correlation between PM parameters and changes in hematocrit, the goal of

this study, we calculated the difference between the hematocrit value last measured before the patient entered the operating room (baseline hematocrit) and the hematocrit value obtained from the ABGA results for each stage of CPB (ΔHct = baseline hematocrit – hematocrit of each CPB stage).

Figure 1. Schematic diagram to calculate PM parameters



The $rScO_2$ values recorded during the entire operation were divided into three stages: pre-CPB, during-CPB and post-CPB. The during-CPB stage was further divided into three stages depending on temperature changes. We computed PM parameters by substituting $rScO_2$, as previously divided, using Varvel et al.'s PM formula. PM, performance measurement; PE, performance error; $rScO_2$, cerebral regional oxygen saturation; CPB, cardiopulmonary bypass; MDPE, median performance error; MDAPE, median absolute performance error.

Statistical analysis

Demographic data, clinical characters, hemodynamic and laboratory profiles, and PM parameters are presented as mean ± SD. Comparisons between acyanotic and cyanotic groups were performed with a paired T-test. Pearson correlation was performed for the correlation between hemodilution for CPB and PM parameters.

Data analysis was carried out using Excel® program (Microsoft 2016) and SPSS software (Version 21), and $P<0.05$ was considered statistically significant. However, $P<0.1$ was also included in the correlation with hematocrit change.

Results

Initially, 100 children who had undergone surgery for congenital heart disease were selected but, due to the lack of some data, 93 children (acyanotic 48, cyanotic 45) were included in the analysis. The reasons for the exclusions were that $rScO_2$ values in some intervals were missing for four children, and some ABGA values were missing for three children.

Patient characteristics and demographic data are summarized in Table 1. There were significant differences between the two groups for preoperative SpO_2 ($P<0.001$) and CPB time ($P<0.001$).

Table 1. Demographic and clinical characteristics of the study cohort

	All (*n* =93)	Acyanotic (*n* =48)	Cyanotic (*n* =45)	P value
Age, month	14.2±20.4	17.3±23.9	10.9±15.2	0.127
Male, %	56 (60.4%)	27 (56.3%)	29 (64.4%)	0.425
Height, cm	72.2±18.6	75.7±20.3	68.4±15.8	0.058
Weight, kg	8.9±5.9	9.8±7.2	7.9±4.0	0.120
Body surface area, m^2	0.41±0.18	0.45±0.22	0.38±0.14	0.077
Preoperative SpO_2, %	92.5±7.9	97.7±1.6	87.0±8.2	< 0.001
CPB time, min	106.7±52.0	85.7±34.4	129.0±58.0	< 0.001

Data are presented as mean ± SD, median with interquartile range, or numbers (%). SpO_2, peripheral capillary oxygen saturation; CPB, cardiopulmonary bypass.

Correlations between PM parameters and changes in hematocrit

The relationship between the change in hematocrit and PM parameters, the subject of this study, is shown in Table 2. In the cyanotic group, there was a significant relationship between MDPE, MDAPE and ΔHct in the during-CPB stage. Figure 2 shows that there is a significant correlation in the cyanotic group between a decrease in hematocrit and a decrease in MDPE. When the CPB period is divided into three stages according to the change in body temperature, the relationship between ΔHct, MDPE and MDAPE is strongest in the rewarming phase of CPB. There was no relationship after CPB termination.

In the acyanotic group, there was a significant relationship between ΔHct and $rScO_2$ at all stages except the pre-CPB stage. MDPE, MDAPE and wobble did not show a significant relationship with ΔHct as a whole. However, as shown in Figure 2, MDPE and ΔHct inversely correlate in the during-CBP stage, unlike in the cyanotic group.

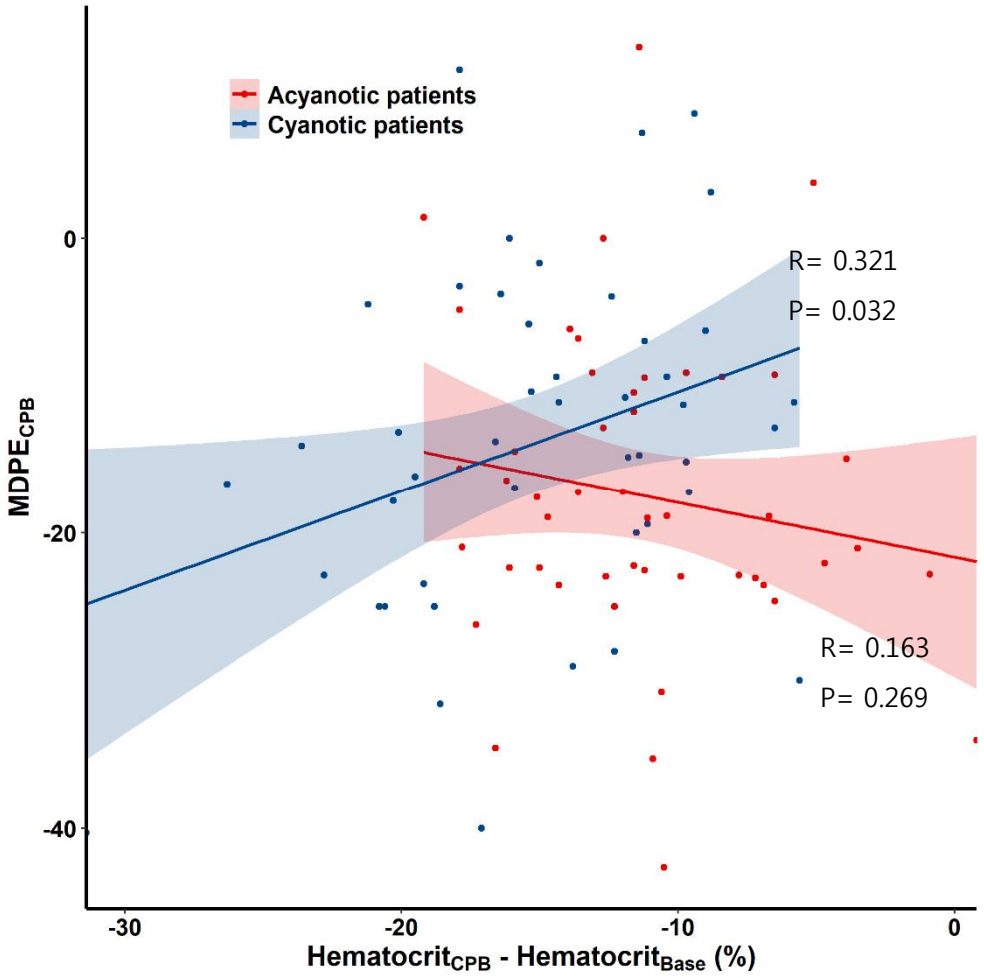
Table 2. Correlation between decrease in hematocrit and performance measurement of cerebral oxygen saturation

	$rScO_2$, %		MDPE, %		MDAPE, %		Wobble, %	
	R	P value	R	P value	R	P value	r	P value
Acyanotic								
Pre-CPB	0.106	0.473	0.034	0.816	0.100	0.498	0.004	0.977
During-CPB	0.517	<0.001**	0.163	0.269	0.197	0.179	0.065	0.659
Cooling CPB	0.397	0.005**	0.079	0.595	0.097	0.510	0.093	0.530
Cold CPB	0.298	0.040**	0.094	0.526	0.161	0.276	0.236	0.106
Rewarming CPB	0.448	0.001**	0.110	0.457	0.117	0.430	0.146	0.322
Post-CPB	0.371	0.009**	0.143	0.333	0.062	0.675	0.251	0.085*
Cyanotic								
Pre-CPB	0.207	0.172	0.217	0.152	0.304	0.042**	0.285	0.058*
During-CPB	0.138	0.366	0.321	0.032**	0.336	0.024**	0.126	0.409
Cooling CPB	0.023	0.883	0.133	0.385	0.008	0.959	0.078	0.608
Cold CPB	0.315	0.035**	0.247	0.102	0.271	0.071*	0.065	0670
Rewarming CPB	0.183	0.230	0.275	0.068*	0.288	0.055*	0.017	0.912
Post-CPB	0.126	0.409	0.080	0.599	0.074	0.629	0.220	0.147

* P value <0.1 ** P value <0.05

$rScO_2$, cerebral regional oxygen saturation; MDPE, median performance error; MDAPE, median absolute performance error; CBP, cardiopulmonary bypass

Figure 2. Scatterplot between the ΔHct and MDPE in the during-CPB stage



Scatterplot demonstrating the relationships between the ΔHct and MDPE in the during-CPB stage by linear regression and Pearson correlation. ΔHct, Δ(Hematocrit$_{CPB}$ – Hematocrit$_{Base}$); MDPE, median performance error; CPB, cardiopulmonary bypass.

PM according to CPB stages

The time-dependent flow of PE, the first step in calculating PM parameters, is shown in Figure 3. The PE values of the two groups are reversed at the start and end of CPB. Before the start of CPB, the PE of the acyanotic group is larger, but after the start of CPB, the PE of the cyanotic group becomes larger. After CPB termination, the PE of the acyanotic group becomes larger again.

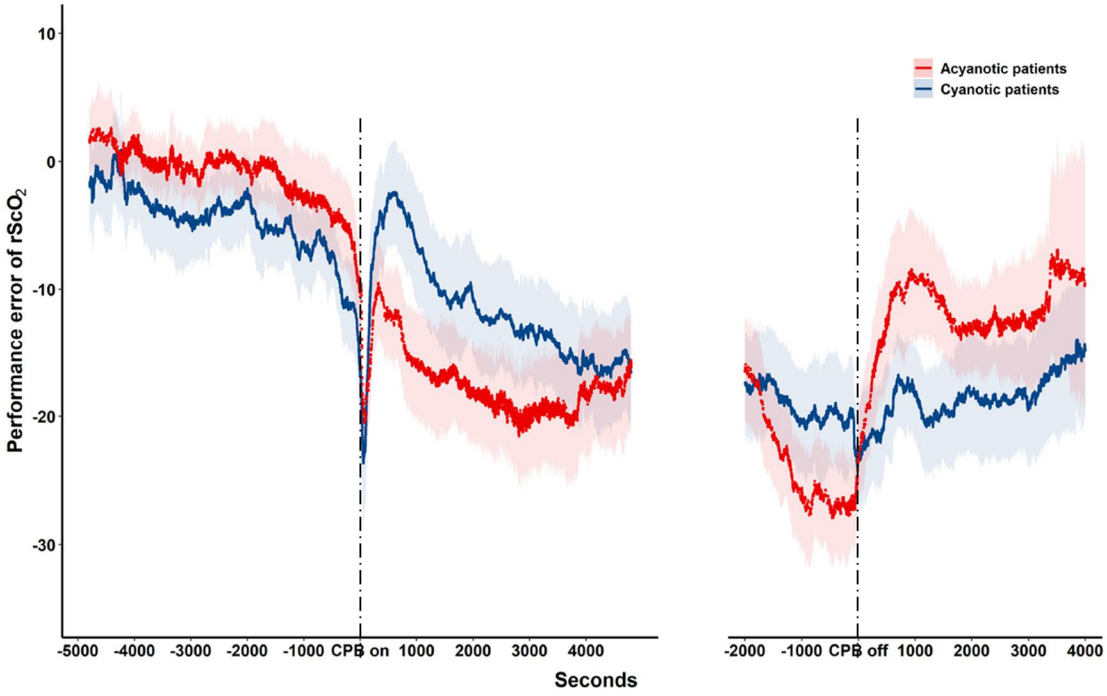
Table 3 shows the PM of $rScO_2$ by CPB stage. In the pre-CPB stage, there was no difference in $rScO_2$ between the acyanotic and cyanotic groups (66.5% vs. 65%). However, in the cyanotic group, MDPE was significantly lower (0% vs. -2.9%, P=0.027) and wobble was larger (6.7% vs. 10.1%, P=0.041) than in the acyanotic group.

In the cooling stage of CPB, $rScO_2$ markedly fluctuated (wobble 30.6% vs. 20.6%) compared to the cold CPB and rewarming stages in both groups. During the cooling stage of CPB and cold CPB, decreases in $rScO_2$ of the cyanotic group were less than in the acyanotic group, which was represented by higher MDPE and smaller MDAPE. In the rewarming stage of CPB, $rScO_2$ was significantly higher in the cyanotic group, showing a higher MDPE and a smaller MDAPE (Figure 4) than in the acyanotic group.

In the post-CPB stage, the cyanotic group had significantly lower $rScO_2$ (59.2% vs. 54.9%, P=0.032), MDPE (-10.5% vs. -18.5%, P=0.002) and larger MDAPE (14% vs. 19.5%, P=0.005)

than the acyanotic group.

Figure 3. Performance error of $rScO_2$ at the start and end points of CPB during surgery.



Performance error flows of acyanotic and cyanotic groups are reversed based on the start and end points of CPB. Shading around performance error flow lines means 95% CI. $rScO_2$, regional cerebral oxygen saturation; CPB, cardiopulmonary bypass.

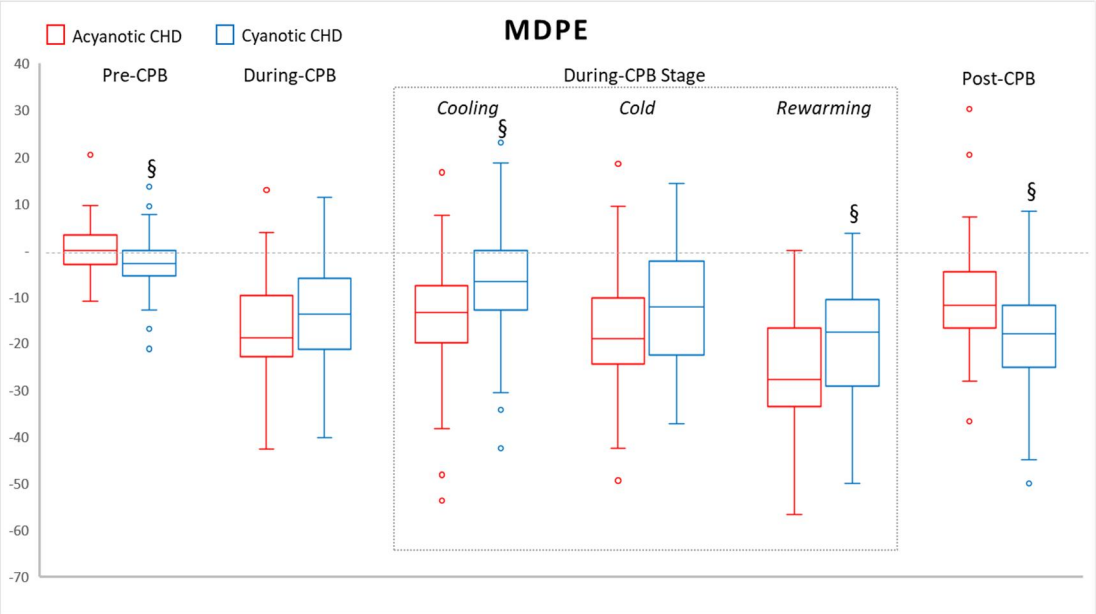
Table 3. Performance measurement of cerebral oxygen saturation according to CPB stages

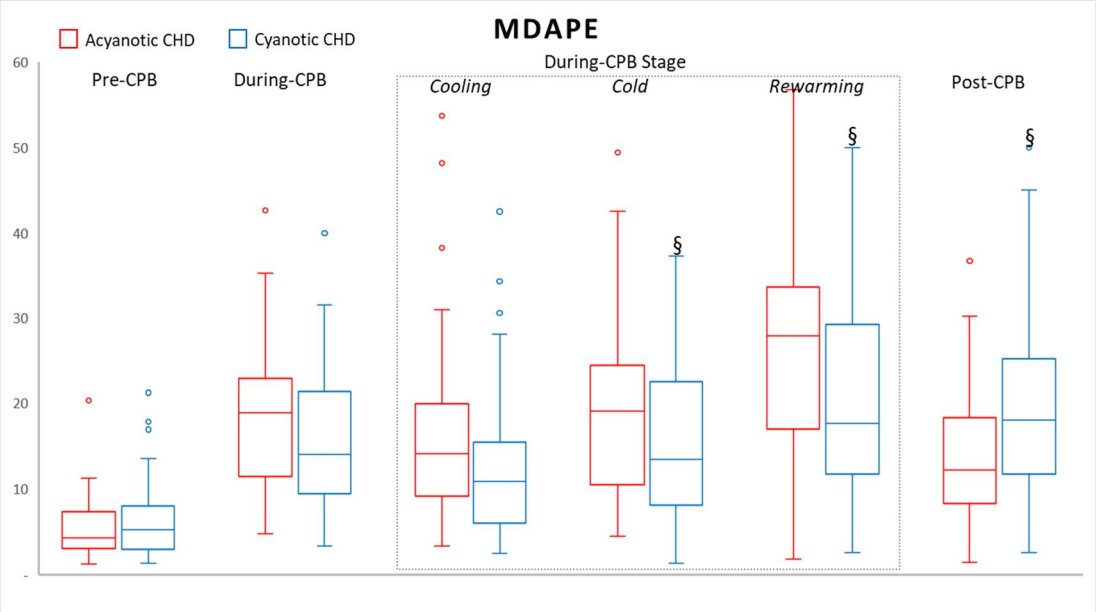
	$rScO_2$, %			MDPE, %			MDAPE, %			Wobble, %		
	Acyanotic	Cyanotic	P-value	Acyanotic	Cyanotic	P-value	Acyanotic	Cyanotic	P-value	Acyanotic	Cyanotic	P-value
Pre-CPB	66.5±8.9	65±8.8	0.436	0±5.8	-2.9±6.5	0.027*	5.3±3.5	6.5±4.5	0.126	6.7±5.6	10.1±9.3	0.041*
During-CPB	54.5±7.9	57.5±7.6	0.069	-17.5±10.4	-13.8±11.5	0.117	18.7±8.3	16.0±8.9	0.138	5.5±2.9	5.7±2.8	0.694
Cooling CPB	57.0±10	61.5±8.4	0.022*	-14.4±12.2	-7.0±13.1	0.006*	16±10.2	12.8±8.6	0.105	30.6±21.6	20.6±18.5	0.020*
Cold CPB	54.7±8.8	58.3±7.9	0.043*	-17.4±12.6	-12.3±11.8	0.052	19.1±9.8	14.9±8.7	0.031*	3.5±2.2	3.6±2.5	0.787
Rewarming CPB	49.1±8.8	53.4±9.1	0.025*	-26.4±12	-20.6±12.5	0.027*	26.6±11.8	21.1±11.9	0.031*	3.1±2.4	3.8±3.1	0.188
Post-CPB	59.2±8.3	54.9±10.3	0.032*	-10.5±11.5	-18.5±12	0.002*	14±7.4	19.5±10.4	0.005*	4.2±2.5	3.9±2.1	0.518

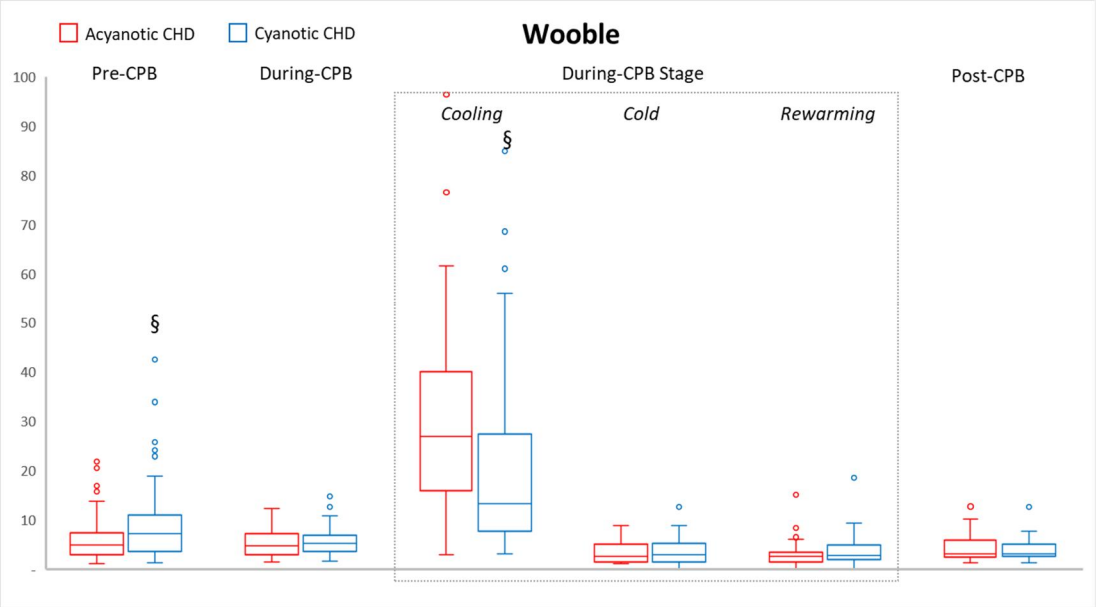
* P value <0.05 vs. acyanotic

Data are presented as mean ± SD. CPB, cardiopulmonary bypass; MDPE, median performance error; MDAPE, median absolute performance error.

Figure 4. Comparison of performance measurements between acyanotic CHD children and cyanotic CHD children using box-plot.







Lower and upper whiskers are minimum and maximum values. Round symbols show the 5th/95th percentile values. §P<0.05 vs acyanotic CHD children. CHD, congenital heart disease; CPB, cardiopulmonary bypass; MDPE, median performance error; MDAPE, median absolute performance error

Hemodynamic and laboratory profiles and their correlation with PM parameter

Table 4 details hemodynamic and laboratory data according to CPB stage, including; mean arterial pressure, heart rate, target temperature, and ABGA results. There was no difference in mean arterial pressure, heart rate, and target temperature between the two groups, but the cyanotic group had a significantly lower PaO_2 and SaO_2 in the pre-CPB and post-CPB stages than the acyanotic group. Also, the cyanotic group had a higher hematocrit concentration in the pre-CPB stage than did the acyanotic group.

The relationship between pH, $PaCO_2$ and performance measurement of $rScO_2$ is shown in Table 5. In the cyanotic group, pH was correlated with $rScO_2$ and wobble during the pre-CPB stage. In the cold stage, both pH and $PaCO_2$ showed a significant relationship with $rScO_2$ and MDPE. In the post-CPB stage, both pH and $PaCO_2$ were correlated with wobble.

In the acyanotic group, pH was correlated with $rScO_2$ during pre-CPB stage. In the cold stage, $PaCO_2$ showed low P-values with $rScO_2$ and MDPE. Also, both pH and $PaCO_2$ were correlated with wobble during the rewarming stage.

Table 4. Hemodynamic and laboratory profiles according to CPB stages

	Pre-CPB		During-CPB						Post-CPB	
			Cooling CPB		Cold CPB		Rewarming CPB			
	Acyanotic	Cyanotic	Acyanotic	Cyanotic	Acyanotic	Cyanotic	Acyanotic	Cyanotic	Acyanotic	Cyanotic
MAP (mmHg)	66.4±12.6	62.7±15.1	50.3±10.1	58.1±9.4	54.3±9.0	57.5±8.1	46.9±8.8	52±9.1	68.9±9.96	70.9±19.7
HR (bpm)	123.5±24.1	120.5±22.5	-	-	-	-	-	-	144.3±25	145.6±26
Target BT (° C)	-	-	-	-	31.0±1.2	30.7±1.3	-	-	-	-
pH	7.4±0.1	7.4±0.1	7.4±0.04	7.35±0.05	7.42±0.05	7.43±0.06	7.42±0.06	7.43±0.09	7.4±0.04	7.4±0.1
PaO_2 (mmHg)	141.0±36.4	80.3±46.5*	279.4±61.9	272±61.6	286.8±34	282.1±36.4	226.9±69.3	254±66.7	148.1±53.5	114.7±59.3*
$PaCO_2$ (mmHg)	39.1±3.6	42.2±7.7	39.2±4.2	43.4±6.2	37.2±4.2	36.3±6.3	36.6±5.6	37±8.4	41.1±4.6	43.6±7.2
SaO_2 (%)	98.8±1.1	90.1±8.5*	100±0.3	99.9±0.4	100	100±0.1	99.4±2.1	99.8±0.7	98.3±2.2	91.1±14.7*
Hematocrit (%)	35.6±3.9	40.1±6.4*	24.3±1.7	25±2.8	26.2±2.4	25.6±2.7	25.6±2.2	26.3±2.8	31.7±3.3	32.5±5.1

* P value <0.05 vs. acyanotic

Data are presented as mean ± SD. CPB, cardiopulmonary bypass; MAP, mean arterial pressure; HR, heart rate; BT, body temperature; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of carbon dioxide tension; SaO_2, arterial blood oxygen saturation; $rScO_2$, cerebral regional oxygen saturation.

Table 5. Correlation between laboratory profiles and performance measurement of cerebral oxygen saturation

	P value with $rScO_2$		P value with MDPE		P value with MDAPE		P value with Wobble	
	Acyanotic	Cyanotic	Acyanotic	Cyanotic	Acyanotic	Cyanotic	Acyanotic	Cyanotic
pH								
Pre-CPB	0.022**	0.095*	0.259	0.047**	0.755	0.085*	0.284	0.035**
During-CPB								
Cooling CPB	0.058*	0.614	0.979	0.123	0.731	0.437	0.863	0.197
Cold CPB	0.051*	<0.001**	0.055*	0.007**	0.318	0.095*	0.107	0.908
Rewarming CPB	0.724	0.301	0.524	0.567	0.464	0.528	0.016**	0.175
Post-CPB	0.633	0.040**	0.662	0.287	0.771	0.158	0.294	0.026**
$PaCO_2$								
Pre-CPB	0.415	0.078*	0.173	0.130	0.700	0.065*	0.490	0.065*
During-CPB								
Cooling CPB	0.042**	0.566	0.864	0.443	0.666	0.356	0.882	0.348
Cold CPB	0.038**	0.003**	0.011**	0.004**	0.035**	0.067*	0.149	0.447
Rewarming CPB	0.302	0.153	0.777	0.389	0.864	0.387	0.001**	0.115
Post-CPB	0.397	0.129	0.449	0.739	0.359	0.691	0.216	<0.001**

* P value <0.1 ** P value <0.05

$rScO_2$, cerebral regional oxygen saturation; MDPE, median performance error; MDAPE, median absolute performance error; CBP, cardiopulmonary bypass; $PaCO_2$, partial pressure of carbon dioxide tension.

Discussion

In this study, we demonstrated that there is a significant relationship between MDPE, MDAPE and ΔHct in the during-CPB stage in cyanotic CHD children. In the pre-CPB stage, there was no difference in $rScO_2$ between the two groups, but MDPE and wobble were different between the groups. Both groups showed a decrease in $rScO_2$ after the start of CPB, although the decrease was less in the cyanotic group. Wobble was very large in both groups in the cooling CPB stage.

Figure 2 shows the correlation between ΔHct and MDPE in entire CPB time. There was a statistically significant relationship only in the cyanotic CHD group; the larger the ΔHct, the lower the MDPE. Since the baseline hematocrit of cyanotic CHD children is higher, ΔHct also increases (located on the left side in the picture relative to acyanotic CHD children), and this rapid change seems to affect $rScO_2$ maintenance. On the other hand, in the acyanotic group, the larger the ΔHct, the higher the MDPE.

Hemodilution in CPB may be an advantage in children with acyanotic CHD who do not normally have a major problem with oxygen delivery. As the viscosity of the blood decreases, the microcirculation flow of organs is improved and risk of hypertension in the high bypass flow reduces. The probability of needing transfusions also reduces (11). However, unlike acyanotic children, hemodilution can be a problem for children with cyanotic CHD because the high hematocrit concentration state, which is an important compensation mechanism for

proper oxygen delivery, does not function.

The importance of increasing hematocrit concentration as a compensation mechanism for cyanosis is evidenced by people living in high altitudes, or chronic hypoxic conditions, where cerebral saturation is not much different from those living in lowlands (12). However, for those who are exposed to chronic hypoxia, little is known about how sudden hematocrit changes might affect cerebral oxygen saturation. Since acute hemodilution occurs in CPB-based cardiac surgery, we investigated whether this sudden change in hematocrit affects $rScO_2$ in patients with cyanotic CHD with high baseline hematocrit.

This study demonstrates that children with cyanotic CHD have significantly lower levels of preoperative peripheral oxygen saturation, but $rScO_2$ is maintained without any difference from children with acyanotic CHD. These results indicate that, even if exposed to chronic hypoxia, $rScO_2$ is maintained normally through an appropriate compensation mechanism, consistent with the results of previous studies (13). However, in the pre-CPB stage (Table 3), there was a significant difference in MDPE and wobble between the two groups. This finding suggests that in cyanotic CHD children, although $rScO_2$ is maintained within the normal range by a compensating mechanism such as increasing hematocrit concentration, the value is not stable and it fluctuates greatly.

When CPB is started, $rScO_2$ values fall in both groups (Table 3), but to a lesser degree in cyanotic children. This condition is maintained for the duration of CPB and is thought to be

the result of exposure to excess oxygen through CPB in cyanotic children who have maintained $rScO_2$ despite chronic hypoxia caused by the heart defect. However, we do not know from this study whether this short-term, sudden, high-concentration oxygen supply has a positive effect on the brain of cyanotic CHD children. The reversal of PE value at the start of CPB, that can be seen in Figure 3, is also due to the relatively slight drop in the cyanotic group relative to the acyanotic group.

Although the $rScO_2$ of the acyanotic group was lower than in the cyanotic group throughout the CPB period, it was significantly higher in the post-CPB period (the PE value also reverses with CPB termination). This is a different result to the absence of divergence in $rScO_2$ between the two groups in the pre-CPB stage and indicates that children with acyanotic CHD recover more rapidly in terms of $rScO_2$. This finding also means that the cyanotic group needs time to adapt to changes in physiology due to surgery, although they have to provide adequate oxygen to their brain at the same time as the CPB ends.

Wobble values in both groups were significantly larger in the cooling phase, which suggests that sudden body temperature deterioration impedes $rScO_2$ maintenance mechanisms and causes serious fluctuations. This effect is not seen at any stage other than in the cooling CPB stage (Figure 4).

In the verification of the relationship with pH, $PaCO_2$, and other factors that could affect $rScO_2$, there were some significant results, even though there were no differences in pH or

$PaCO_2$ between the two groups. Both acyanotic and cyanotic groups showed a relationship with PM parameters in the cold CPB stage, which can be seen as a reflection of the importance of maintaining the acid-base balance in CPB. The lower P-value in the cyanotic group, in particular, suggests that these children need more careful maintenance (Table 5).

To measure $rScO_2$, we used NIRS, a non-invasive real-time tissue oxygen saturation meter. The value derived from NIRS reflects the oxygen supply and metabolic rate of the brain, which is especially useful for cardiopulmonary bypass (14, 15). Unlike pulse oximetry, which measures the oxygen saturation of arterial blood, NIRS does not distinguish between arterial and venous blood, and it reflects the oxygen saturation of the whole tissue, including arteries, veins and capillaries (16). Since 70% to 85% of cerebral blood flow is venous blood, the $rScO_2$ value mainly reflects the oxygen saturation of the venous blood, and is an index reflecting the oxygen supply and extraction of the brain (17, 18).

In our study, we adapted PM to determine the fluctuation of $rScO_2$ in children with CHD. This method measures the bias, accuracy, and time-dependent variability of $rScO_2$ during cardiac surgery by using MDPE, MDAPE, and wobble. PM was originally a method used in pharmacokinetic studies to investigate the difference between the target concentration of the drug and the actual measurement (10). Some studies have applied the PM method to determine how the bispectral index or blood pressure during anesthesia fluctuate based on the target value (19, 20).

There are some limitations in this study. Firstly, Varvel et al.'s paper (10), which we used as our method, proposed divergence as one of the PM analysis methods, but we did not use that indicator here. As divergence is a measure that indicates the expected systemic time-related change in PE in the original drug concentration measurement, it was excluded from the method because it was not suitable for this study in which the target value for $rScO_2$ was not set. If we had directly measured the oxygen saturation of the jugular vein, we might have been able to set the target $rScO_2$. Secondly, hematocrit, pH, and gas partial pressure may be different depending on the sampling time of ABGA. Thirdly, the actual oxygen consumption of the brain was not directly measured and could not be related to the outcome of the patient. The information analyzed should be supplemented in future studies.

Conclusion

The $rScO_2$ of children with cyanotic CHD was maintained in the normal range through compensatory mechanism including hemoconcentration, although variability was greater than children with acyanotic CHD. Hemodilution in CPB has advantages in children with acyanotic CHD. However, in children with cyanotic CHD, cerebral oxygen variability may be affected by degree of hemodilution in CPB, particularly in the rewarming phase. These results emphasize the importance of avoiding excessive hemodilution. Further study is needed to clarify the implication of cerebral oxygen variability for neurodevelopmental outcomes after cyanotic CHD surgery.

Reference

1. Dent CL, Spaeth JP, Jones BV, Schwartz SM, Glauser TA, Hallinan B, et al. Brain magnetic resonance imaging abnormalities after the Norwood procedure using regional cerebral perfusion. J Thorac Cardiovasc Surg. 2005;130(6):1523-30.

2. Lim JM, Kingdom T, Saini B, Chau V, Post M, Blaser S, et al. Cerebral oxygen delivery is reduced in newborns with congenital heart disease. J Thorac Cardiovasc Surg. 2016;152(4):1095-103.

3. Neunhoeffer F, Hofbeck M, Schlensak C, Schuhmann MU, Michel J. Perioperative Cerebral Oxygenation Metabolism in Neonates with Hypoplastic Left Heart Syndrome or Transposition of the Great Arteries. Pediatric cardiology. 2018.

4. Xu K, Lamanna JC. Chronic hypoxia and the cerebral circulation. Journal of applied physiology (Bethesda, Md : 1985). 2006;100(2):725-30.

5. Greeley WJ, Ungerleider RM, Smith LR, Reves JG. The effects of deep hypothermic cardiopulmonary bypass and total circulatory arrest on cerebral blood flow in infants and children. J Thorac Cardiovasc Surg. 1989;97(5):737-45.

6. Kurth CD, Steven JM, Nicolson SC, Chance B, Delivoria-Papadopoulos M. Kinetics of cerebral deoxygenation during deep hypothermic circulatory arrest in neonates. Anesthesiology. 1992;77(4):656-61.

7. Sapire KJ, Gopinath SP, Farhat G, Thakar DR, Gabrielli A, Jones JW, et al. Cerebral oxygenation during warming after cardiopulmonary bypass. Critical care medicine. 1997;25(10):1655-62.

8. Pua HL, Bissonnette B. Cerebral physiology in paediatric cardiopulmonary bypass. Canadian journal of anaesthesia = Journal canadien d'anesthesie. 1998;45(10):960-78.

9. Lee HC, Jung CW. Vital Recorder-a free research tool for automatic recording of high-resolution time-synchronised physiological data from multiple anaesthesia devices.

Scientific reports. 2018;8(1):1527.

10. Varvel JR, Donoho DL, Shafer SL. Measuring the predictive performance of computer-controlled infusion pumps. Journal of pharmacokinetics and biopharmaceutics. 1992;20(1):63-94.

11. Murphy GS, Hessel EA, 2nd, Groom RC. Optimal perfusion during cardiopulmonary bypass: an evidence-based approach. Anesthesia and analgesia. 2009;108(5):1394-417.

12. Furian M, Latshang TD, Aeschbacher SS, Ulrich S, Sooronbaev T, Mirrakhimov EM, et al. Cerebral oxygenation in highlanders with and without high-altitude pulmonary hypertension. Experimental physiology. 2015;100(8):905-14.

13. Kussman BD, Laussen PC, Benni PB, McGowan FX, Jr., McElhinney DB. Cerebral Oxygen Saturation in Children With Congenital Heart Disease and Chronic Hypoxemia. Anesthesia and analgesia. 2017;125(1):234-40.

14. Murkin JM, Arango M. Near-infrared spectroscopy as an index of brain and tissue oxygenation. British journal of anaesthesia. 2009;103 Suppl 1:i3-13.

15. Zheng F, Sheinberg R, Yee MS, Ono M, Zheng Y, Hogue CW. Cerebral near-infrared spectroscopy monitoring and neurologic outcomes in adult cardiac surgery patients: a systematic review. Anesthesia and analgesia. 2013;116(3):663-76.

16. Kurth CD, Steven JM, Nicolson SC, Jacobs ML. Cerebral oxygenation during cardiopulmonary bypass in children. J Thorac Cardiovasc Surg. 1997;113(1):71-8; discussion 8-9.

17. Bickler PE, Feiner JR, Rollins MD. Factors affecting the performance of 5 cerebral oximeters during hypoxia in healthy volunteers. Anesthesia and analgesia. 2013;117(4):813-23.

18. Watzman HM, Kurth CD, Montenegro LM, Rome J, Steven JM, Nicolson SC. Arterial and venous contributions to near-infrared cerebral oximetry. Anesthesiology. 2000;93(4):947-53.

19. Hemmerling TM, Arbeid E, Wehbe M, Cyr S, Taddei R, Zaouter C. Evaluation of a novel closed-loop total intravenous anaesthesia drug delivery system: a randomized controlled trial. British journal of anaesthesia. 2013;110(6):1031-9.

20. Lee HC, Ryu HG, Jung CW. Performance measurement of intraoperative systolic arterial pressure to predict in-hospital mortality in adult liver transplantation. Scientific reports. 2017;7(1):7030.

Abstract (Korean)

배경 만성적인 저산소증에 노출되는 청색증형 선천성 심기형 환아들은 헤마토크릿 농도를 높임으로써 적정 산소 공급을 유지시킨다. 이러한 환아들이 심장 교정 수술 중 심폐우회로를 사용할 경우, 급격한 혈액 희석으로 인해 뇌산소포화도 ($rScO_2$) 값이 요동칠 수 있다. 이 연구의 목표는 심폐우회로를 이용한 심장 수술을 하는 선천성 심기형 환아에서 뇌산소포화도의 변동 정도를 수행 오류 (Performance Measurement) 방법으로 분석해보고, 그 변동값이 헤마토크릿 농도 변화와 연관이 있는지 살펴보는 것이다.

방법 뇌산소포화도 감시를 하며 심폐우회로를 이용한 심장 수술을 받은 환아들을 대상으로 하였다. 수행 오류 방법의 지표들인 MDPE, MDAPE, wobble 값들을 뇌산소포화도 측정값을 바탕으로 계산하였다. 측정 구간은 심폐우회로 전, 중간, 후 로 나눈 뒤 심폐우회로 중간 구간을 다시 체온 변화에 따라 세 단계로 나누었다. 이 계산된 지표들이 헤마토크릿 농도의 변화 정도와 연관성이 있는지 알아보았다.

결과 총 100명의 환아 중, 93명 (비청색증형 48명, 청색증형 45명)이 최종 결과에 포함되었다. 심폐우회로 시작 전에는 두 그룹 간의 뇌산소포화도의 차이는 없었지만 청색증형 그룹에서 MDPE는 유의하게 낮고 (0% vs -2.9%, P=0.027), wobble은 컸다(6.7% vs. 10.1%, P=0.041). 청색증형 그룹에서 심폐우회로 전체 시간 동안의 MDPE (P=0.032), MDAPE (P=0.024)와 헤마토크릿 농도 변화 사이에 유의한 연관성

을 나타냈다. 심폐우회로 종료 후에는 청색증형 그룹에서 뇌산소포화도 (59.2% vs 54.9%, P=0.032)와 MDPE (-10.5% vs -18.5%, P=0.002)는 낮고, MDAPE (14% vs 19.5%, P=0.005)는 컸다.

결론 청색증형 선천성 심장 기형 환아들은 헤마토크릿 농도 증가와 같은 보상기전을 통해 뇌산소포화도를 정상 범위로 유지하지만, 그 변동성은 비청색증형 보다 크다. 이러한 변동성은 혈액 희석이 이루어지는 심폐우회로 사용시 더 심해지므로, 심폐우회로 시기에 지나친 혈액 희석은 피하는 것이 좋겠다.

핵심어 뇌산소포화도, 선천성 심기형, 심폐우회로