Regional Cerebral Oxygen Saturation and Estimated Oxygen Extraction Ratio as Predictive Markers of Major Adverse Events in Pediatric Cardiac Patients

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Research Article

Keywords: Spectroscopy, Near-Infrared, oxygen consumption, heart defects, congenital, cardiopulmonary bypass, child

Posted Date: January 16th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2471176/v1

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Abstract

Regional cerebral oxygen saturation (ScO\textsubscript{2}) determined by near-infrared spectroscopy, monitoring both arterial and venous blood oxygenation of the brain, could reflect the balance between oxygen delivery and consumption. The aim of this study was to determine the predictabilities of ScO\textsubscript{2} and estimated oxygen extraction ratio (eO\textsubscript{2}ER) with outcomes in pediatric patients with congenital heart disease (CHD). This study was a two-center, retrospective study of patients at 12 months of age or younger with CHD who underwent cardiac surgery. The primary outcome was a composite of one or more major adverse events (MAEs) after surgery: death from any cause, circulatory collapse that needed cardiopulmonary resuscitation, and requirement for extracorporeal membrane oxygenation. Based on the assumptions of arterial to venous blood ratio, eO\textsubscript{2}ER was calculated. A total of 647 cases were included in this study. MAEs occurred in 16 patients (2.5%). There were significant differences in the average post-bypass ScO\textsubscript{2} [46.61 (40.90, 52.05) vs. 58.52 (51.52, 66.08), p < 0.001] and the average post-bypass eO\textsubscript{2}ER [0.66 (0.60, 0.78) vs. 0.52 (0.43, 0.61), p < 0.001] between patients with MAEs and patients without MAEs. Area under the receiver operating curve (AUROC) of the average of post-bypass ScO\textsubscript{2} was 0.818 (95% confidence interval: 0.747–0.889), AUROC of the average of post-bypass eO\textsubscript{2}ER was 0.783 (0.697–0.870) and AUROC of post-bypass maximum serum lactate level was 0.635 (0.525–0.746). Both ScO\textsubscript{2} and eO\textsubscript{2}ER, especially after weaning off bypass, are acceptable predictive markers for predicting MAEs after cardiac surgery in infants.

Introduction

Pediatric patients with congenital heart disease need strict management for the balance between systemic oxygen supply and consumption. Although mixed venous saturation (SvO\textsubscript{2}) is one of the useful markers for estimating the balance between oxygen delivery and consumption, a true mixed venous blood sample should be drawn from the pulmonary artery and it is difficult to measure true SvO\textsubscript{2} for patients with an intracardiac shunt. Due to those limitations, central venous saturation (ScvO\textsubscript{2}), measured from the tip of the central venous line, is widely used as a surrogate of SvO\textsubscript{2}. However, frequent blood sampling and measurements cause anemia, especially in small children, and a central venous line with oximetry to measure ScvO\textsubscript{2} continuously has a larger diameter, which might be inappropriate for a patient with small vessels with possibly a high risk of thrombosis.

Near-infrared spectroscopy (NIRS) is a noninvasive technology that continuously monitors regional oxygenation. Assessment of regional cerebral oxygen saturation (ScO\textsubscript{2}) using NIRS has been used for pediatrics as well as adults to ensure oxygenation of the brain during cardiac surgery. Since ScO\textsubscript{2} reflects both arterial and venous blood oxygenation of the brain and cerebral venous blood drains to the superior vena cava, it could reflect ScvO\textsubscript{2} and the balance between oxygen delivery and consumption [1,2]. Studies in which the usefulness for ScO\textsubscript{2} monitoring systemic circulation was assessed showed that a decrease in ScO\textsubscript{2} is associated with postoperative acute kidney injury, duration of mechanical ventilation, and
length of stay in an intensive care unit among pediatric cardiac patients [3–5]. Furthermore, estimated saturation of the venous component from $\text{ScO}_2$ might be a better surrogate of $\text{ScvO}_2$ than $\text{ScO}_2$ itself [6].

While studies have been carried out to assess postoperative $\text{ScO}_2$ in patients with congenital heart disease, there is little evidence regarding the associations of intraoperative $\text{ScO}_2$ as a marker of systemic circulation with oxygen balance and patients’ prognosis. Since hemodynamic instability due to impaired cardiac function, anatomical cardiac abnormality and the effects of anesthetic and surgical procedures is profound in pediatric cardiac patients, efforts to balance oxygen demand and oxygen consumption in a timely manner are essential. We hypothesized that $\text{ScO}_2$ during anesthesia reflects $\text{ScvO}_2$ and is associated with a poor outcome. The aims of this study were 1) to determine the trend of $\text{ScO}_2$ and estimated oxygen extraction ratio during anesthesia in pediatric patients with congenital heart disease who needed cardiopulmonary bypass and 2) to determine the predictabilities of those with patients’ outcomes.

Methods

Design and study population

This study was a two-center (Okayama University Hospital and Fukuoka Children's Hospital, Japan) retrospective study of patients with congenital heart disease who underwent cardiac surgery and were admitted to the pediatric cardiac intensive care unit (PCICU) during the period from May 2018 to August 2021. We included patients who were 12 months of age or younger. We excluded patients who were on extracorporeal membrane oxygenation (ECMO) at the end of surgery, patients who underwent a second or subsequent cardiac operation(s), patients who underwent cardiac surgery without CPB, and patients without monitoring of $\text{ScO}_2$ during surgery. The study was approved by the Okayama University Hospital Ethics Committee (Institutional Review Board Approval Number: 2111-004, approval date: Sep 24th, 2021) and Fukuoka Children's Hospital Ethics Committee (Institutional Review Board Approval Number: 2121-1198, approval date: Oct 12th, 2021), and the need for informed consent was waived. All regulations and measures of ethics and confidentiality were handled in accordance with the Declaration of Helsinki.

Study variables and data sources

Patients’ information and laboratory data were stored in a central server and subsequently exported for further analyses through a medical data recording system, Prescient CDM (FUJIFILM Medical IT Solutions Co., Ltd., Tokyo, Japan), in each institution, and additional information was obtained from electronic patient medical records.

$\text{ScO}_2$ was measured by commercially available devices, and the measurements during anesthesia were recorded minute-by-minute in the CDM system. Estimated jugular venous oxygen saturation (eSjvO$_2$) was calculated on the basis of an assumption and reference of a certain arterial to venous volume ratio in the
brain adopted in each device. For instance, as an accuracy validation of O3 Regional Oximeter (Masimo, Irvine, CA) was based on a 30% arterial to 70% venous ratio (25405692)[7], we calculated eSjvO² using ScO² and peripheral oxygen saturation (SpO²) according to the following equation: eSjvO² = (ScO² - SpO² * 0.3) / 0.7 (25313967)(28599970)[6,8]. For cases with ScO2 measured by INVOS (Somanetics, Troy, MI) and tissue oxygenation index (TOI) measured by a NIRO spectrometer (Hamamatsu Photonics, Japan), a 25% arterial to 75% venous ratio, referring to previous validation studies [9–11], was used for the calculation. Then minute-by-minute estimated oxygen extraction ratio (eO₂ER) was calculated as 1 – (eSjvO² / SpO²). Variability of ScO² was also calculated using the root mean of successive squared differences [12,13]. Averages of ScO² (ScO₂ave), eO₂ER (eO₂ERave), and variability of ScO² before CPB and after CPB were used for analyses. Types of surgery were classified on the basis of the Risk-Adjusted Classification for Congenital Heart Surgery Version 1 (RACHS-1) category [14]. Patients were classified to subgroups based on average SpO₂ before starting CPB: Pre-CPB average SpO₂ ≤ 92% [cyanotic congenital heart disease (CHD) group] and pre-CPB average SpO₂ > 92% (non-cyanotic CHD group).

The primary outcome was a composite of one or more of the following major adverse events (MAEs) that occurred within 7 days after cardiac surgery: death from any cause, circulatory collapse that needed cardiopulmonary resuscitation, and requirement for ECMO. The secondary outcomes were serum lactate level at pediatric cardiac intensive care unit (PCICU) admission (Lac_base), vasoactive inotropic score (VIS) at PCICU admission (VIS_base), maximum serum lactate level for the first 24 hours (Lac₂₄max), maximum VIS for the first 24 hours (VIS₂₄max), ventilator-free days for the first 30 days after surgery, and PCICU length of stay. The VIS was calculated as dopamine (mcg/kg/min) + dobutamine (mcg/kg/min) + 100*epinephrine (mcg/kg/min) + 100*norepinephrine (mcg/kg/min) + 10*milrinone (mcg/kg/min) + 10000*vasopressin (U/kg/min) [15].

**Statistical analysis**

Data are presented as frequency and proportions or median (IQR, interquartile range; 25% quartile, 75% quartile) as appropriate. For groupwise comparisons of continuous variables, the Wilcoxon rank sum test (two groups) or Kruskal-Wallis test (more than two groups) was used. For categorical variables, Fisher’s exact test or the chi-square test was used as appropriate.

Multivariable logistic regression analyses were performed to study the associations of ScO₂, variability of ScO₂, and eO₂ER with MAEs. Variables included in the models were weight, cyanotic CHD, and RACHS-1 score.

Receiver operating curves (ROCs) for predicting MAEs were used to assess the predictability of ScO₂, variability of ScO₂, and eO₂ER. Area under the receiver operating curve (AUROC) was used to find the best predictor of MAEs among those parameters. Youden index was used to find the optimal cutoffs of those parameters. Since some studies suggested that evidence generated with one NIRS device may not be applied to other manufacturers’ devices due to measurement variation [16], subgroup analyses classifying data based on NIRS devices were performed.
All statistical comparisons were two-sided and a significance level was defined as a P value of less than 0.05. All statistical analyses were performed using R 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Participants

A total of 1255 patients who underwent cardiac surgery were considered to be eligible for this study. After excluding 608 patients based on exclusion criteria, 647 patients were included and analyzed in a cohort (Fig. 1). The Median age and median weight of the patients were 77 (IQR 15, 188) days and 4.03 (IQR 3.00, 6.06) kg, respectively. Among the patients included in the whole cohort, an O3 regional oximeter, INVOS, and NIRO spectrometer were used in 231 patients (35.7%), 4 patients (0.6%), and 414 patients (64.0%), respectively. MAEs occurred in 16 patients (2.5%). Characteristics of the patients and outcomes in the patients in the cohort are shown in Table 1.
Table 1
Patients’ characteristics and intraoperative near-infrared spectroscopy-related values and comparison between patients with major adverse events and patients without major adverse events

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All cases (n = 647)</th>
<th>MAE (n = 16)</th>
<th>No MAE (n = 631)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, month, [IQR]</td>
<td>76.83 [15.00, 187.75]</td>
<td>27.21 [10.25, 52.56]</td>
<td>80.83 [15.00, 189.00]</td>
<td>0.039</td>
</tr>
<tr>
<td>Weight, kg [IQR]</td>
<td>4.03 [3.00, 6.06]</td>
<td>3.08 [2.78, 3.63]</td>
<td>4.09 [3.01, 6.13]</td>
<td>0.023</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>376 (58.1)</td>
<td>9 (56.2)</td>
<td>367 (58.2)</td>
<td>1</td>
</tr>
<tr>
<td>RACHS-1 [IQR]</td>
<td>3.00 [2.00, 3.00]</td>
<td>3.00 [3.00, 4.00]</td>
<td>3.00 [2.00, 3.00]</td>
<td>0.005</td>
</tr>
<tr>
<td>Duration of operation, minute [IQR]</td>
<td>249.00 [200.00, 316.00]</td>
<td>262.50 [248.50, 320.75]</td>
<td>248.00 [199.50, 316.00]</td>
<td>0.316</td>
</tr>
<tr>
<td>Duration of cardiopulmonary bypass, minute [IQR]</td>
<td>117.50 [83.00, 165.00]</td>
<td>124.00 [86.50, 174.00]</td>
<td>116.00 [83.00, 165.00]</td>
<td>0.784</td>
</tr>
<tr>
<td>Pre-CPB ScO$_2$ave, [IQR]</td>
<td>58.74 [53.19, 64.90]</td>
<td>48.60 [40.13, 64.17]</td>
<td>58.89 [53.40, 64.92]</td>
<td>0.01</td>
</tr>
<tr>
<td>Pre-CPB variability of ScO$_2$, [IQR]</td>
<td>1.76 [1.34, 2.66]</td>
<td>2.43 [1.70, 3.22]</td>
<td>1.75 [1.34, 2.64]</td>
<td>0.134</td>
</tr>
<tr>
<td>Pre-CPB eO$<em>2$ER$</em>{ave}$, [IQR]</td>
<td>0.48 [0.39, 0.59]</td>
<td>0.62 [0.35, 0.77]</td>
<td>0.48 [0.39, 0.58]</td>
<td>0.14</td>
</tr>
<tr>
<td>Pre-CPB Lac$_{max}$, mmol/L [IQR]</td>
<td>1.00 [0.78, 1.44]</td>
<td>1.31 [0.87, 1.92]</td>
<td>1.00 [0.78, 1.44]</td>
<td>0.115</td>
</tr>
<tr>
<td>Post-CPB ScO$_2$ave, [IQR]</td>
<td>58.18 [50.66, 65.86]</td>
<td>46.61 [40.90, 52.05]</td>
<td>58.52 [51.52, 66.08]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Post-CPB variability of ScO$_2$, [IQR]</td>
<td>1.31 [0.94, 2.39]</td>
<td>1.43 [1.15, 2.48]</td>
<td>1.31 [0.94, 2.37]</td>
<td>0.428</td>
</tr>
<tr>
<td>Post-CPB eO$<em>2$ER$</em>{ave}$, [IQR]</td>
<td>0.52 [0.44, 0.62]</td>
<td>0.66 [0.60, 0.78]</td>
<td>0.52 [0.43, 0.61]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Post-CPB Lac$_{max}$, mmol/L [IQR]</td>
<td>2.40 [1.78, 3.90]</td>
<td>2.80 [2.35, 3.45]</td>
<td>2.33 [1.74, 3.95]</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Abbreviations: MAE, major adverse event; IQR, interquartile range; RACHS-1, Risk-Adjusted Classification for Congenital Heart Surgery Version 1; CPB, cardiopulmonary bypass; ScO$_2$ave, average regional cerebral oxygen saturation; ScO$_2$, regional cerebral oxygen saturation; eO$_2$ER$_{ave}$, average estimated oxygen extraction ratio; Lac$_{max}$, maximum serum lactate level

Pre- and post-cardiopulmonary bypass near-infrared spectroscopy-related values
eO2ERave after weaning off CPB was significantly higher than that before CPB [0.52 (IQR: 0.44, 0.62) vs. 0.48 (IQR: 0.39, 0.59), p < 0.001], and the variability of ScO2 after weaning off CPB was significantly lower than that before CPB [1.31 (IQR: 0.94, 2.39) vs. 1.76 (IQR: 1.34, 2.66), p < 0.001]. There was no significant difference between pre-CPB ScO2ave and post-CPB ScO2ave [58.2 (IQR: 50.7, 65.9) vs. 58.7 (IQR: 53.2, 64.9), p = 0.28] (Fig. 2).

Comparison between patients with major adverse events and patients without major adverse events

Patients with MAEs were significantly younger than those without MAEs, and patients with MAEs had significantly smaller weight and higher RACHS-1 score. There were significant differences in pre-CPB ScO2ave, post-CPB ScO2ave, and post-CPB eO2ERave, but not in other NIRS-related values before CPB or after CPB, between patients with MAEs and patients without MAEs. Table 1 shows a comparison of patients’ characteristics and NIRS values between patients with MAEs and patients without MAEs.

The results of multivariable logistic regression analyses with incidence of MAEs as the outcome are shown in eTable 1. After adjusting for weight, cyanotic CHD, and RACHS-1 score, there were significant differences in odds of pre-CPB eO2ERave [odds ratio (OR): 1.04, 95% CI: 1.01–1.08, p = 0.006] and post-CPB eO2ERave (OR: 1.05, 95% CI: 1.02–1.08, p = 0.001) for MAEs. Similarly, there were significant differences in odds of pre-CPB ScO2ave (OR: 0.93, 95% CI: 0.88–0.97, p = 0.003) and post-CPB ScO2ave (OR: 0.93, 95% CI: 0.89–0.97, p < 0.001) for MAEs.

Predictive performances for major adverse events

Results of unadjusted ROC analyses for predicting MAEs are shown in Fig. 3: AUROC of pre-CPB ScO2ave was 0.689 [95% confidence interval (CI): 0.515–0.864], AUROC of pre-CPB variability of ScO2 was 0.609 (95% CI: 0.466–0.753), AUROC of pre-CPB eO2ERave was 0.608 (95% CI: 0.411–0.805) and AUROC of pre-CPB maximum lactate level (Lacmax) was 0.612 (95% CI: 0.474–0.750). AUROC of post-CPB ScO2ave was 0.818 (95% CI: 0.747–0.889), AUROC of post-CPB variability of ScO2 was 0.558 (95% CI: 0.439–0.677), AUROC of post-CPB eO2ERave was 0.783 (95% CI: 0.697–0.870) and AUROC of post-CPB Lacmax was 0.635 (95% CI: 0.525–0.746). The optimal cutoff of post-CPB eO2ERave for MAEs was 0.66. Results of unadjusted ROC analyses for predicting MAEs in subgroups of patients with the use of each NIRS device are shown in eTable 2.

Associations with other outcomes

The median Lacadm and Lac24max values were 2.63 (IQR: 1.70, 3.91) mmol/L and 3.19 (IQR: 2.30, 4.80) mmol/L, respectively. The median VISadm and VIS24max values were 4.86 (IQR: 2.03, 7.80) and 5.16 (IQR: 2.05, 8.30), respectively. Figure 4 shows a correlation matrix between NIRS-related values and serum lactate levels during anesthesia and secondary outcomes during the PCICU stay.

Discussion
In this retrospective study, we found that eO$_2$ER and variability of ScO$_2$ changed significantly across CPB. There were significant differences in pre-CPB ScO$_{2ave}$, post-CPB ScO$_{2ave}$, and post-CPB eO$_2$ER$_{ave}$ between patients with MAEs and patients without MAEs. ScO$_{2ave}$ and eO$_2$ER$_{ave}$ after weaning off CPB had relatively large AUROC for predicting MAEs.

While several studies have been carried out to assess the associations of preoperative [17] and postoperative [4,5] ScO$_2$ monitoring with outcomes in patients with CHD, especially neurodevelopment [18–21], only a few studies have been carried out to assess intraoperative ScO$_2$-related values as a potential surrogate of oxygen supply-demand balance and their predictability for patients’ outcomes in patients with CHD. Zulueta et al. scored duration and degree of ScO$_2$ reduction during cardiac surgery in 22 children at ages of less than 12 months and reported significant associations of the ScO$_2$ reduction score with intraoperative central venous saturation, cardiac index, extraction of oxygen and postoperative low cardiac output syndrome [22]. Suemori et al. conducted a retrospective study including 399 pediatrics who underwent cardiac surgery and found that mean TOI of 5 minutes after the operation prior to ICU admission was significantly associated with major morbidity and mortality [23]. Aly et al. carried out a study in 75 patients with CHD who underwent cardiac surgery within the first month of life to assess the prognostic accuracy of TOI. According to their prospective cohort study, patients who survived had a significantly higher average TOI at 60 minutes off CPB than that for patients who died [19]. Since estimated saturation of the venous component from ScO$_2$ might be a better surrogate of ScvO$_2$ than ScO$_2$ itself [6], we calculated eO$_2$ER from minute-by-minute SpO$_2$ and ScO$_2$ measurements and found a relatively large AUROC of eO$_2$ER as well as ScO$_2$, especially after weaning from CPB, for MAEs. Our finding of a significantly higher post-CPB eO$_2$ER than pre-CPB eO$_2$ER may imply that eO$_2$ER detects a negative hemodynamic impact by CPB and, thus, impaired oxygen supply-demand balance. Furthermore, relatively high AUROC of post-CPB eO$_2$ER and that of post-CPB ScO$_2$, compared with those before CPB, might suggest that impaired post-CPB oxygen supply-demand balance is a sign of poor postoperative outcomes.

There are other possibilities to explain the predictability of eO$_2$ER and ScO$_2$ for MAEs. For instance, patients with cyanosis might have low ScO2 and low ScO$_2$ was therefore associated with poor outcomes. However, subgroup analyses by classifying patients based on oxygen saturation before CPB still demonstrated similar predictive performances in both subgroups, suggesting that eO$_2$ER could be used as a predictive marker for MAEs both in infants with cyanosis and infants without cyanosis. We also need to be aware that eO$_2$ER represents brain tissue oxygen extraction, rather than systemic oxygen extraction, on the basis of the calculation [24]. The high cutoff, considering a surrogate of systemic oxygen extraction ratio, of post-CPB eO$_2$ER of 0.66 might be due not only to the fatal outcomes, MAEs, but also to the difference in the targeted tissue. For instance, eO$_2$ER could be related to cerebral blood flow away from systemic blood flow and systemic oxygen supply. Some studies have shown that infants with CHD might have cerebrovascular instability and impaired cerebral autoregulation, possibly leading to high eO$_2$ER [25,26]. Furthermore, patients with diastolic “run-off” could have decreased cerebral blood flow.
flow, leading to decreased ScO\textsubscript{2} and increased eO\textsubscript{2}ER [27]. In those contexts, eO\textsubscript{2}ER has an acceptable predictive performance, possibly not due to being a surrogate of systemic oxygen supply-demand balance but for other reasons such as impaired cerebral autoregulation or anatomical reasons. In fact, there are conflicting data regarding estimation of mixed venous or central venous saturation by ScO\textsubscript{2} among pediatric cardiac surgery patients [2,28–32]. Since one of the possible reasons for the disagreement between the two measurements is no correction of ScO\textsubscript{2} for “arterial contamination” [6], the eO\textsubscript{2}ER in our study was calculated for the correction. However, we still cannot rule out the possibility that the favorable predictability of eO\textsubscript{2}ER might originate from factors other than a surrogate of real O\textsubscript{2}ER.

Variability of ScO\textsubscript{2} is an issue of interest for this population. Recent studies have shown that patients following cardiac surgery had reduced ScO\textsubscript{2} variability [12], which has been shown to be associated with poor neurodevelopmental outcomes [13]. The hypothesis is that reduced variability of ScO\textsubscript{2} might signify impaired autoregulation or inadequacy of compensatory mechanisms of cardiovascular systems [13]. Our data showed that ScO\textsubscript{2} variability after CPB was significantly lower than that before CPB, indicating the possibility of impaired autoregulation of cardiovascular systems due to CPB or CPB-related factors. On the other hand, the predictive ability of ScO\textsubscript{2} variability for MAEs was consistently low throughout cardiac surgery, and the association between ScO\textsubscript{2} variability and neurodevelopment was not assessed in our study. We also found poor correlations between NIRS-related values and other outcomes including serum lactate level, VIS, ventilator-free days, and PCICU length of stay. Although those secondary outcomes were clinically important, those outcomes could be variable depending on institutional strategies. Different strategies for target hemoglobin level and transfusion, medications for inotropes and dilation, fluid management, sedation and muscle relaxants would result in differences in those secondary outcomes. Lack of those data makes it difficult to stratify patients and to obtain generalizability.

There are several limitations in this study. First, this study was a retrospective study focusing on infants with CHD after cardiac surgery and the findings cannot be generalized to other populations. However, the results of this retrospective study, in which a large amount of data recorded minute-by-minute in two leading institutions in the area of pediatric cardiac surgery in Japan was analyzed, would have better generalization than the results of a single center study. Second, there were three NIRS instruments used for ScO\textsubscript{2} monitoring in the institutions, and all of the data were combined on the basis of an assumption and calibration of a certain arterial to venous volume ratio in the brain adopted in each device. However, the devices use different technologies and methods to provide cerebral oxygenation data, and several studies have shown positive correlations but disagreements between devices [33,34]. Some studies also suggested that evidence generated with one NIRS device may not be applied to other manufactures’ devices [16]. Subgroup analyses classifying data based on the NIRS device, however, showed consistent results. Third, the association between eO\textsubscript{2}ER and MAEs would not indicate causal inference. The aim of this study was to determine the predictive ability of ScO\textsubscript{2}-related values for patients’ outcomes, not to assess the effect of high eO\textsubscript{2}ER on patients’ outcomes. Thus, admitting that there might be factors that
would have an impact on $\text{eO}_2\text{ER}$, such as serum hemoglobin level, partial pressure of carbon dioxide and temperature, their contributions as confounding factors is not within the focus of our study.

**Conclusion**

$\text{eO}_2\text{ER}$ and variability of $\text{ScO}_2$ are significantly different before and after CPB. Both $\text{ScO}_2$ and $\text{eO}_2\text{ER}$, especially after weaning off CPB, are acceptable predictive markers for predicting MAEs after cardiac surgery in infants.

**Declarations**

Ethics approval and consent to participate: The study protocol was approved by the Okayama University Hospital Ethics Committee and and Fukuoka Children's Hospital Ethics Committee. The committees waived any requirement for informed consent due to this study utilizing an existing database.

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

Funding: The authors declare that they have no funding.

ACKNOWLEDGEMENTS

Not applicable

**References**


Figures

1255 patients who underwent cardiac surgery during the study period

608 patients excluded for the following reasons
  • 7 patients who were on ECMO at the end of surgery
  • 332 patients who underwent the second or subsequent cardiac operation(s) during the study period
  • 205 patients who underwent cardiac surgery without CPB
  • 64 patients without monitoring of ScO₂ during surgery

647 patients in the primary cohort

Figure 1

Flow chart
Abbreviations: ECMO, extracorporeal membrane oxygenation; CPB, cardiopulmonary bypass; ScO₂, regional cerebral oxygen saturation

**Figure 2**

Comparison of near-infrared spectroscopy-related values before cardiopulmonary bypass and after cardiopulmonary bypass.

Abbreviations: ScO₂, Regional cerebral oxygen saturation; eO₂ER, estimated oxygen extraction ratio; CPB, cardiopulmonary bypass; *, p< 0.05; **, p< 0.01; *** p< 0.001
Figure 3

Receiver operating curves of near-infrared spectroscopy-related values before cardiopulmonary bypass and after cardiopulmonary bypass for major adverse events.

Abbreviations: CPB, cardiopulmonary bypass; ScO$_{2\text{ave}}$, average regional cerebral oxygen saturation; eO$_2$ER, estimated oxygen extraction ratio; Lac$_{\text{max}}$, maximum serum lactate level
Figure 4

Correlation matrix between near-infrared spectroscopy-related values and serum lactate levels during anesthesia and secondary outcomes.

Dark color in the squares indicates a stronger correlation between the row and the column variables; the number inside each square corresponds to the correlation coefficient.
Abbreviations: CPB, cardiopulmonary bypass; ScO_{ave}, average regional cerebral oxygen saturation; ScO_{2}, regional cerebral oxygen saturation; eO_{2}ER_{ave}, average estimated oxygen extraction ratio; Lac_{max}, maximum serum lactate level; Lac_{adm}, serum lactate level at admission; VIS_{adm}, vasoactive inotropic score at admission; Lac_{24max}, maximum serum lactate level for the first 24 hours; VIS_{24max}, maximum vasoactive inotropic score for the first 24 hours; Vent-free days, ventilator-free days; LOS, length of stay in pediatric cardiac intensive care unit

Supplementary Files

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