

学 位 論 文

Cerebral hemoglobin oxygenation in children  
with congenital heart disease

香川大学大学院医学系研究科  
機能構築医学専攻

寺田 一也



## Cerebral hemoglobin oxygenation in children with congenital heart disease

Kazuya Terada, MD<sup>1</sup>; Shinji Nakamura, MD, DMSc<sup>2</sup>; Yasuhiro Nakao, MD<sup>2</sup>; Keisuke Fukudome, MD<sup>1</sup>; Yuichi Miyagi, MD<sup>1</sup>; Tatsuya Onishi, MD<sup>1</sup>; Takashi Kusaka, MD, DMSc<sup>3</sup>

<sup>1</sup> Division of Pediatric Cardiology, Shikoku Medical Center for Children and Adults, Japan

<sup>2</sup> Maternal Perinatal Center, Faculty of Medicine, Kagawa University, Japan

<sup>3</sup> Department of Pediatrics, Faculty of Medicine, Kagawa University, Japan

**Corresponding author:** Takashi Kusaka

Department of Pediatrics, Faculty of Medicine, Kagawa University

1750-1 Ikenobe, Miki-cho, Kita-gun, Kagawa 761-0793, Japan

Tel.: +81-87-891-2171; Fax: +81-87-891-2172

E-mail: kusaka@med.kagawa-u.ac.jp

### **Counts**

Text pages: 12 pages

Word count: 3,227 words

Reference pages: 4 pages

Tables: 5 tables

Figures: 2 figures

## **Abstract**

**Background:** It is important to identify the pathological characteristics of cerebral circulation and oxygen metabolism at the bedside in children with congenital heart disease (CHD) to prevent neurodevelopmental impairments. The brain regional oxygen saturation index (rSO<sub>2</sub>) can be easily obtained at the bedside with near-infrared spectroscopy and has been widely used in the management of children with CHD in recent years.

**Methods:** To determine if the rSO<sub>2</sub> before or after CHD surgery is a good predictor of cerebral oxygen metabolism, we investigated the impact of different clinical variables on the correlation between rSO<sub>2</sub> and reference values under steady ratios of hemoglobin oxygen saturation in the internal jugular vein (SjvO<sub>2</sub>) or femoral artery (SaO<sub>2</sub>) (0.75:0.25, 0.66:0.34, and 0.50:0.50) in 186 children with CHD undergoing cardiac catheterization.

**Results:** In three patient groups—double ventricles before surgery, double ventricles after surgery, and single ventricle before surgery—there were significant relationships between rSO<sub>2</sub> and the reference values of SO<sub>2</sub> under all three steady ratios of SjvO<sub>2</sub> and SaO<sub>2</sub>. No relationship with the reference values was found for the single ventricle after surgery group.

**Conclusions:** rSO<sub>2</sub> is useful for assessing cerebral oxygenation in children with CHD, but knowledge of the underlying cardiac pathology in CHD, especially in the case of a single ventricle after surgery, is important for the correct interpretation of rSO<sub>2</sub> measurements obtained using near-infrared spectroscopy.

## **Keywords**

Brain, heart disease, hemoglobin, near-infrared spectroscopy, oxygen consumption.

## **Introduction**

In survivors of congenital heart disease (CHD), several types of neurodevelopmental impairment are common and are a primary factor in the evaluation of clinical outcomes (1-4). It is important to identify the pathological characteristics of the cerebral circulation and oxygen metabolism at the bedside in children with CHD to prevent neurodevelopmental impairments.

Near-infrared spectroscopy (NIRS) using near-infrared light (700–900 nm) enables changes to be detected in the oxygenation of hemoglobin (Hb) and water in biological tissue. It is safe and permeates the tissues adequately and has recently been applied to the functional evaluation of circulation and oxygenation status. NIRS is clinically applicable in children because the light more readily permeates a child's head than an adult's, because of its small size and low scattering. Also, the measured values are less influenced by layered structures such as the scalp, skull, and cerebrospinal fluid (5, 6).

The INVOS 5100C Cerebral/Somatic Oximeter (Covidien Japan, Tokyo) derives the “regional oxygen saturation index” (rSO<sub>2</sub>) using spatially resolved spectroscopy (SRS) measurements and the photon diffusion theory (7,8). Brain rSO<sub>2</sub> measurements can be easily obtained using NIRS at the bedside, and it has been widely used in the management of children with CHD in recent years (9-11). Some reports indicate that rSO<sub>2</sub> during or after CHD surgery is a good predictor of postoperative outcome and neurodevelopmental impairment (1, 12, 13) but others have failed to show its usefulness for assessing the prognosis of children with CHD (14-16).

rSO<sub>2</sub> depends on the state of cerebral blood oxygenation and flow and on the state of cerebral oxygen metabolism, which is also affected by various factors, including blood Hb levels, blood pressure, cardiac output, and intracranial pressure. Theoretically, rSO<sub>2</sub>

is mainly affected by the ratio of the arterial contribution to that of venous blood and the Hb oxygenation in these vessels (17-22). Clinical variables are assumed to also affect rSO<sub>2</sub> measurements, and local cerebral blood flow and metabolism in the measurement area may be affected by the CHD or related surgical procedures. However, the relationships between rSO<sub>2</sub> and values of clinical variables under several steady ratios of internal jugular venous Hb oxygen saturation (SjvO<sub>2</sub>) and arterial Hb oxygen saturation (SaO<sub>2</sub>) have not yet been investigated in children with different forms of CHD. This information would be very useful in the clinical setting for evaluating cerebral oxygen metabolism. Because rSO<sub>2</sub> and SaO<sub>2</sub> can be measured easily and noninvasively at the bedside, we can indirectly calculate the value of SjvO<sub>2</sub> by using both the rSO<sub>2</sub> and SaO<sub>2</sub> values and the ratio of the arterial contribution to that of venous blood. SjvO<sub>2</sub> is very useful for estimating cerebral oxygen metabolism in CHD patients. In addition, knowledge of other factors affecting the value of rSO<sub>2</sub> would be useful for its validation.

This retrospective study had three objectives: (1) to evaluate the relationship between rSO<sub>2</sub> and not only SjvO<sub>2</sub>, but also Hb oxygen saturation in other regions in children with CHD; (2) to assess the relationships between rSO<sub>2</sub> and values of clinical variables under steady ratios of SjvO<sub>2</sub> and SaO<sub>2</sub>; (3) and to identify the impact of different clinical variables on the correlation between the rSO<sub>2</sub> and steady ratios of SjvO<sub>2</sub> and SaO<sub>2</sub> in children with CHD before and after surgery.

### **Patients and methods**

We retrospectively reviewed data from 188 pediatric patients (115 male, 73 female) between 0 and 15 years of age who underwent cardiac catheterization for CHD from January 2015 to September 2016. The diagnoses of the enrolled patients were aortic

stenosis, atrial septal defect, atrioventricular septal defect, double outlet right ventricle, hypoplastic left heart syndrome, single left ventricle, pulmonary atresia, patent ductus arteriosus, single right ventricle, tricuspid atresia, total anomalous pulmonary venous return/connection/drainage, transposition of the great arteries, tetralogy of Fallot, ventricular septal defect, and other CHD (Table 1).

During cardiac catheterization, all patients were administered sevoflurane inhalational anesthesia under respiratory management with fentanyl. At the time of catheterization, the optical sensor of the INVOS 5100C system (Covidien Japan) was attached to the right side of the patient's forehead to measure the  $rSO_2$ . In addition, blood was sampled from the right internal jugular vein, superior vena cava, inferior vena cava, and pulmonary artery using a wedge catheter and from the femoral artery using a catheter sheath. Blood gas analysis was performed with an ABL 800 FLEX blood gas analyzer (Radiometer Co., Tokyo, Japan).

### **Relationships between $rSO_2$ and other parameters**

We evaluated the relationship between  $rSO_2$  and not only Hb oxygen saturation in the internal jugular vein ( $SjvO_2$ ), but also Hb oxygen saturation in the superior vena cava ( $SsvcO_2$ ), inferior vena cava ( $SivcO_2$ ), pulmonary artery ( $SpaO_2$ ), and femoral artery ( $SaO_2$ ). We also evaluated the relationship between  $rSO_2$  and arterial oxygen tension ( $PaO_2$ ), carbon dioxide tension ( $PaCO_2$ ), Hb value (bHb), heart rate (HR), mean arterial blood pressure (MABP), and central venous pressure (CVP).

### **Relationships between $rSO_2$ and $SO_2$ reference values under steady ratios of $SjvO_2$ and $SaO_2$**

The reference values under steady S<sub>jv</sub>O<sub>2</sub>:S<sub>a</sub>O<sub>2</sub> ratios of 0.75:0.25, 0.66:0.34, and 0.50:0.50 were calculated as  $SO_2(0.75:0.25) = 0.75 \times S_{jv}O_2 + 0.25 \times S_aO_2$ ,  $SO_2(0.66:0.34) = 0.66 \times S_{jv}O_2 + 0.34 \times S_aO_2$ , and  $SO_2(0.50:0.50) = 0.5 \times S_{jv}O_2 + 0.5 \times S_aO_2$ , respectively.

### **Impact of different clinical variables on the correlation between rSO<sub>2</sub> and steady ratios of S<sub>jv</sub>O<sub>2</sub> and S<sub>a</sub>O<sub>2</sub>**

Because double-ventricle CHD is similar to physiological circulation while single-ventricle CHD indicates a specific and distinct circulation, CHD patients were divided into five subgroups: 1) double ventricles before surgery; 2) double ventricles after surgery (endocardial repair); 3) single ventricle before surgery; 4) single ventricle after surgery (Fontan); and 5) others. In each group except “others”, we evaluated the relationships between rSO<sub>2</sub> and S<sub>jv</sub>O<sub>2</sub>, S<sub>a</sub>O<sub>2</sub>, and the reference values of SO<sub>2</sub> under steady ratios of S<sub>jv</sub>O<sub>2</sub> and S<sub>a</sub>O<sub>2</sub>. In addition, in each group, we evaluated the relationship of rSO<sub>2</sub> with bHb, HR MABP, and CVP.

Next, to determine if there was any difference in the interpretation of rSO<sub>2</sub> in CHD without or with cyanosis, participants were divided into non-cyanotic and cyanotic groups. Cyanosis was defined as an S<sub>a</sub>O<sub>2</sub> less than 82%. CHD patients from groups 1 to 4 were divided into the following four subgroups and re-evaluated: 1) without cyanosis before surgery; 2) without cyanosis after surgery; 3) with cyanosis before surgery; and 4) with cyanosis after surgery.

This clinical study was performed as a collaboration between Shikoku Medical Center for Children and Adults and Covidien Japan under the name "Research on the Utility of INVOS 5100C during Pediatric Cardiac Catheterization". The study was

approved by the Ethics Committee of Shikoku Medical Center for Children and Adults as “The comparison of jugular venous oxygen saturation with rSO<sub>2</sub> in children” (H27–50). Written informed consent was obtained from the families of the patients.

### **Statistical analysis**

Results are expressed as the mean (standard deviation). Spearman's rank-order correlation of the paired data was applied and correlation coefficients and *P* values calculated. *P* < 0.05 was considered significant and a Spearman's correlation was postulated if the r-value was > 0.4. Statistical analysis was performed with the GraphPad Prism 8 software package (GraphPad Software, San Diego, CA).

### **Results**

In total, 188 children with CHD underwent cardiac catheterization in our hospital during the study period. Two patients were excluded because NIRS measurements were not performed correctly. Finally, data from 186 children were analyzed. The number of patients for each CHD diagnosis in the five groups were 72 in the double ventricles before surgery group, 66 in the double ventricles after surgery group, 21 in the single ventricle before surgery group, 18 in the single ventricle after surgery group, and 9 others (data not shown). Table 1 summarizes the cardiac pathologies in the study population and Table 2 shows the demographic and physiological data for the cardiac catheterization procedures.

The correlation between rSO<sub>2</sub> and S<sub>ijv</sub>O<sub>2</sub> was significant in all cases (*P* < 0.001, *r* = 0.483). In addition, correlations of rSO<sub>2</sub> with S<sub>svc</sub>O<sub>2</sub> and S<sub>ivc</sub>O<sub>2</sub> were also significant (*P* < 0.0001 and *r* = 0.500 and *P* < 0.0001 and *r* = 0.412, respectively). However, correlations of rSO<sub>2</sub> with S<sub>pa</sub>O<sub>2</sub> and S<sub>a</sub>O<sub>2</sub> were not significant (Figure 1). There were also no

significant relationships of rSO<sub>2</sub> with PaCO<sub>2</sub>, bHb or CVP, but there were significant positive associations of rSO<sub>2</sub> with MABP ( $P < 0.0001$ ,  $r = 0.426$ ) and a significant negative association between rSO<sub>2</sub> and HR ( $P < 0.0001$ ,  $r = -0.459$ ).

Correlations of rSO<sub>2</sub> with SO<sub>2</sub> (0.75:0.25), SO<sub>2</sub> (0.66:0.34), and SO<sub>2</sub> (0.50:0.50) were significant in all cases (all  $P < 0.0001$ ; Figure 2, Table 3).

In three groups, namely, the double ventricles before surgery, double ventricles after surgery, and single ventricle before surgery groups, there were significant relationships between rSO<sub>2</sub> and SjvO<sub>2</sub> and between rSO<sub>2</sub> and the reference values of SO<sub>2</sub> under all three steady ratios of SjvO<sub>2</sub> and SaO<sub>2</sub>. Only the single ventricle before surgery group showed a significant relationship between rSO<sub>2</sub> and SaO<sub>2</sub> ( $P < 0.003$ ,  $r = 0.611$ ). However, in the single ventricle after surgery group, there were no significant relationships between rSO<sub>2</sub> and SjvO<sub>2</sub> or between rSO<sub>2</sub> and the reference values of SO<sub>2</sub> under steady ratios of SjvO<sub>2</sub> and SaO<sub>2</sub> (Figure 2, Table 3). Furthermore, there was a significant negative association between rSO<sub>2</sub> and HR in these groups, except double ventricles after surgery, and there were significant positive relationships of rSO<sub>2</sub> with MABP in the double ventricles before and after surgery groups (Table 4).

In the before and after surgery without cyanosis groups, there were significant relationships between rSO<sub>2</sub> and SjvO<sub>2</sub> and between rSO<sub>2</sub> and the reference values of SO<sub>2</sub> under all three steady ratios of SjvO<sub>2</sub> and SaO<sub>2</sub>. However, in the before and after surgery with cyanosis groups, there were no significant relationships between rSO<sub>2</sub> and SjvO<sub>2</sub> or between rSO<sub>2</sub> and the reference values of SO<sub>2</sub> under steady ratios of SjvO<sub>2</sub> and SaO<sub>2</sub> (Table 5).

## **Discussion**

The main findings in this study are as follows. First, there were relationships of  $rSO_2$  with  $SjvO_2$ ,  $SsvcO_2$ , and  $SivcO_2$  in patients with CHD. There were also relationships of  $rSO_2$  with  $SO_2$  (0.75:0.25),  $SO_2$  (0.66:0.34), and  $SO_2$  (0.50:0.50), with no apparent differences in the  $r$  level among these three relationships. In subgroup analysis, the double ventricles before surgery, double ventricles after surgery, and single ventricle before surgery groups showed significant relationships between  $rSO_2$  and the reference values of  $SO_2$  under all three steady ratios of  $SjvO_2$  and  $SaO_2$ , unlike the single ventricle after surgery group.

Several types of NIRS systems have been developed: 1) continuous wave spectroscopy (CWS), which is used to specifically estimate changes in the Hb concentration from an initial measurement; 2) full spectral spectroscopy (FSS), which is used to measure the full NIR spectral range; 3) time-resolved spectroscopy (TRS), which measures the transit time of each photon through the tissue of interest; 4) phase-modulated spectroscopy (PMS), which measures amplitude signals for phase, intensity, and depth of modulation after passage; and 5) SRS, which is used to determine the slope of the light attenuation versus distance at a point distant from the source using a continuous wave. FSS, TRS, PMS, and SRS can all be used to measure cerebral Hb oxygen saturation ( $ScO_2$ ). In this study, we measured  $rSO_2$  by using an SRS system. Note that  $rSO_2$  is the unique name for the INVOS 5100C system and is equivalent to  $ScO_2$ .

$ScO_2$  measured using NIRS is based on the assumption that the cephalic region is composed of homogenous tissue, representing a mixed vascular Hb oxygen saturation of arteries, arterioles, capillaries, and veins in the brain. The factors responsible for changes in  $ScO_2$  are mainly the ratio of the contribution of arterial blood to that of venous blood and the Hb oxygenation in these vessels. Using a newborn piglet model, we previously estimated the percentage contributions of arterial and venous blood to  $ScO_2$  as 25% and

75%, respectively (17). In a later study, we found the quantitative arterial and venous ratios corresponding to  $ScO_2$  values with TRS measurements under normoxia to be 34% and 66%, respectively (18). These results were almost identical to those reported by Brun et al. and Ito et al., who found that the ratio of arterial to venous blood was 1:2 (19, 23). In 20 anesthetized children, the ratio was 16:84, but it differed considerably among the participants, ranging from 40:60 to 0:100 (20).

$rSO_2$  had a stronger positive correlation with  $SjvO_2$ ,  $SsvcO_2$ , and  $SivcO_2$  in all patients with CHD, but there were no relationships of  $rSO_2$  with  $SpaO_2$  and  $SaO_2$ . Also, the double ventricles before surgery, double ventricles after surgery, and single ventricle before surgery groups exhibited significant relationships between  $rSO_2$  and  $SjvO_2$ . Several studies have examined  $rSO_2$  as a noninvasive surrogate of  $SjvO_2$ . Although the correlation is usually statistically significant, the correlation coefficient is less than 0.5 and shows a wide range of agreement (association strength from 0.3 to 0.9) (7, 9, 24-26). For children with CHD, some reports are in good agreement regarding the relationship between  $rSO_2$  and  $SjvO_2$  or  $SsvcO_2$  (21, 25, 26). Nagdyman et al. (25) compared two different NIRS systems, the NIRO 200 and INVOS 5100, in 31 children with CHD. Both revealed a significant correlation of the  $rSO_2$  with  $SjvO_2$  and  $SscvO_2$  values, with  $rSO_2$  and  $SjvO_2$  showing a significant correlation ( $r = 0.83$ ,  $P < 0.0001$ ) and  $rSO_2$  and  $SsvcO_2$  showing an even stronger correlation ( $r = 0.93$ ,  $P < 0.0001$ ). Ricci et al. (26) reported that  $rSO_2$  had a fair correlation with  $SsvcO_2$  ( $r = 0.37$ ,  $P < 0.001$ ) in 100 newborn patients who underwent cardiac surgery for CHD. The relationship between  $rSO_2$  and  $SsvcO_2$  was unchanged when patients with cyanotic and acyanotic CHD were compared and  $rSO_2$  was lower than  $SsvcO_2$  at a  $PaCO_2$  level below 31 mmHg.

Correlations of  $rSO_2$  with  $SO_2$  (0.75:0.25),  $SO_2$  (0.66:0.34), and  $SO_2$  (0.50:0.50)

were also significant in all patients and in the three subgroups. These results are based on the fact that the INVOS 5100C system uses a ratio of 75% venous to 25% arterial blood (27). Another study also reported a good correlation between rSO<sub>2</sub> and the reference tissue Hb oxygen saturation ( $0.7 \times \text{SjvO}_2 + 0.3 \times \text{SaO}_2$ ) in 57 children undergoing cardiac catheterization ( $r = 0.72, P < 0.001$ ) (21).

In the single ventricle after surgery group, there were no significant relationships between rSO<sub>2</sub> and the reference values of SO<sub>2</sub> under steady ratios of SjvO<sub>2</sub> and SaO<sub>2</sub>. It is unclear why there were no relationships in this group. The pathogenesis of the CHD itself, the impact of surgery on cerebral circulation and metabolism, or the impact of cerebral injury may have affected the changes in rSO<sub>2</sub> or SjvO<sub>2</sub> measurements. Regarding the CHD itself, if extracerebral blood in the jugular bulb was not negligible, it would increase SjvO<sub>2</sub> due to minimal oxygen extraction from extracranial tissue because of the vascular malformation present in complex CHD. If the capillary blood volume was not negligible, it would give a false high or low ratio of arteries and veins because chronic hypoxia increases brain microvessel density. It is possible that the capillary blood volume may not have been negligible (20). Regarding surgery, aortic-to-pulmonary collaterals associated with the Fontan procedure represent a low resistance runoff of systemic flow into the pulmonary bed, which diverts blood from the developing brain to the lungs, and decrease cerebral blood flow (28). Some brain pathologies such as stroke, regional brain death, and carotid arterial stenosis may decouple the relationships between regional and global oxygenation parameters as well as alter the anatomical ratios of veins and arteries (22). There are reports that rSO<sub>2</sub> does not reflect changes in jugular bulb oximetry in the case of head injury (29-31). Forehead NIRS interrogates the frontal lobes supplied by the superficial branches of the anterior and middle cerebral arteries. It is possible that

hypoxia-ischemia occurs in territories supplied by the deeper branches of the anterior and middle cerebral arteries or the vertebrobasilar system without any change in the measured frontal  $rSO_2$  (9). In addition, surgical procedures that occlude the carotid artery may disrupt the arterial and venous ratio, particularly if the brain hemisphere collateral perfusion is poor. Therefore, knowledge of the child's condition in terms of a single ventricle after surgery is important for interpreting  $rSO_2$  measurements.

In cyanotic patients before and after surgery, we were also unable to find a correlation between  $rSO_2$  and  $SO_2$  under all three steady ratios of  $SjvO_2$  and  $SaO_2$  (Table 5). One of the reasons for this result is that cyanotic patients have cerebral arterial vasodilation and therefore cannot have a correlation between  $rSO_2$  and  $SO_2$  under steady ratios of  $SjvO_2$  and  $SaO_2$ . This can be explained based on our previous results in a newborn piglet model under hypoxic conditions ( $FiO_2 = 10\%$ ), in which the estimated ratio of NIRS signal contributions from arterial and venous blood of 52:48 showed an increased arterial signal compared with the ratio of 25:75 under normoxic conditions (17).

There are several limitations to this study. First, the small sample size of patients with CHD limited appropriate analysis. In addition, because of the sample size and differences in the time before and after surgery, we were unable to make comparisons across each CHD group. The heterogeneity of each CHD group may also limit the analyses across groups.

In conclusion,  $rSO_2$  is useful for assessing cerebral oxygenation in children with CHD, but knowledge of the form of CHD, particularly a single ventricle after surgery, is important for interpreting  $rSO_2$  measurements on NIRS.

**Acknowledgements**

This study was financially supported by Grants-in-Aid for Scientific Research (KAKENHI) from the Japan Society for the Promotion of Science JSPS (Grant numbers: 16K10092, 17K10178, 17K10179, and 19K08253).

**Disclosure**

The authors declare no conflicts of interest.

**Authors' contributions**

KT and TK conceived and designed this study; KT, KF, YM, and TO collected and analyzed data; SN and YN performed the statistical analysis and drafted the manuscript; TK critically reviewed the manuscript and supervised the whole study process. All authors read and approved the final manuscript.

## References

1. Aly SA, Zurakowski D, Glass P, Skurow-Todd K, Jonas RA, Donofrio MT. Cerebral tissue oxygenation index and lactate at 24 hours postoperative predict survival and neurodevelopmental outcome after neonatal cardiac surgery. *Congenit. Heart Dis.* 2017; 12: 188-95.
2. Bellinger DC, Wypij D, Kuban KC, et al. Developmental and neurological status of children at 4 years of age after heart surgery with hypothermic circulatory arrest or low-flow cardiopulmonary bypass. *Circulation* 1999; 100: 526-32.
3. Miller G, Egli KD, Contant C, Baylen BG, Myers JL. Postoperative neurologic complications after open heart surgery on young infants. *Arch. Pediatr. Adolesc. Med.* 1995; 149: 764-8.
4. Bellinger DC, Jonas RA, Rappaport LA, et al. Developmental and neurologic status of children after heart surgery with hypothermic circulatory arrest or low-flow cardiopulmonary bypass. *N. Engl. J. Med.* 1995; 332: 549-55.
5. Fukui Y, Ajichi Y, Okada E. Monte carlo prediction of near-infrared light propagation in realistic adult and neonatal head models. *Appl. Opt.* 2003; 42: 2881-7.
6. Kusaka T, Isobe K, Yasuda S, et al. Evaluation of cerebral circulation and oxygen metabolism in infants using near-infrared light. *Brain Dev.* 2014; 36: 277-83.
7. Abdul-Khaliq H, Troitzsch D, Berger F, Lange PE. Regional transcranial oximetry with near infrared spectroscopy (NIRS) in comparison with measuring oxygen saturation in the jugular bulb in infants and children for monitoring cerebral oxygenation. *Biomed. Tech. (Berl.)* 2000; 45: 328-32.
8. Gagnon RE, Macnab AJ, Gagnon FA, Blackstock D, LeBlanc JG. Comparison of two spatially resolved NIRS oxygenation indices. *J. Clin. Monit. Comput.* 2002; 17:

385-91.

9. Zaleski KL, Kussman BD. Near-infrared spectroscopy in pediatric congenital heart disease. *J. Cardiothorac. Vasc. Anesth.* 2020; 34: 489-500.
10. Thewissen L, Caicedo A, Lemmers P, Van Bel F, Van Huffel S, Naulaers G. Measuring near-infrared spectroscopy derived cerebral autoregulation in neonates: From research tool toward bedside multimodal monitoring. *Front. Pediatr.* 2018; 6: 117.
11. Cheng HH, Ferradal SL, Vyas R, et al. Abnormalities in cerebral hemodynamics and changes with surgical intervention in neonates with congenital heart disease. *J. Thorac. Cardiovasc. Surg.* 2020; 159: 2012-21.
12. Chakravarti SB, Mittnacht AJ, Katz JC, Nguyen K, Joashi U, Srivastava S. Multisite near-infrared spectroscopy predicts elevated blood lactate level in children after cardiac surgery. *J. Cardiothorac. Vasc. Anesth.* 2009; 23: 663-7.
13. Hansen JH, Schlangen J, Voges I, et al. Impact of afterload reduction strategies on regional tissue oxygenation after the Norwood procedure for hypoplastic left heart syndrome. *Eur. J. Cardiothorac. Surg.* 2014; 45: e13-9.
14. Hirsch JC, Charpie JR, Ohye RG, Gurney JG. Near infrared spectroscopy (NIRS) should not be standard of care for postoperative management. *Semin. Thorac. Cardiovasc. Surg. Pediatr. Card. Surg. Annu.* 2010; 13: 51-4.
15. Simons J, Sood ED, Derby CD, Pizarro C. Predictive value of near-infrared spectroscopy on neurodevelopmental outcome after surgery for congenital heart disease in infancy. *J. Thorac. Cardiovasc. Surg.* 2012; 143: 118-25.
16. Claessens NHP, Jansen NJG, Breur J, et al. Postoperative cerebral oxygenation was not associated with new brain injury in infants with congenital heart disease. *J. Thorac. Cardiovasc. Surg.* 2019; 158: 867-77.e1.

17. Kusaka T, Isobe K, Nagano K, et al. Quantification of cerebral oxygenation by full-spectrum near-infrared spectroscopy using a two-point method. *Comp. Biochem. Physiol. A Mol. Integr. Physiol.* 2002; 132: 121-32.
18. Ijichi S, Kusaka T, Isobe K, et al. Quantification of cerebral hemoglobin as a function of oxygenation using near-infrared time-resolved spectroscopy in a piglet model of hypoxia. *J. Biomed. Opt.* 2005; 10: 024026.
19. Brun NC, Moen A, Borch K, Saugstad OD, Greisen G. Near-infrared monitoring of cerebral tissue oxygen saturation and blood volume in newborn piglets. *Am. J. Physiol.* 1997; 273: H682-6.
20. Watzman HM, Kurth CD, Montenegro LM, Rome J, Steven JM, Nicolson SC. Arterial and venous contributions to near-infrared cerebral oximetry. *Anesthesiology* 2000; 93: 947-53.
21. Kussman BD, Laussen PC, Benni PB, McGowan FX Jr., McElhinney DB. Cerebral oxygen saturation in children with congenital heart disease and chronic hypoxemia. *Anesth. Analg.* 2017; 125: 234-40.
22. Benni PB, Chen B, Dykes FD, et al. Validation of the CAS neonatal NIRS system by monitoring vv-ECMO patients: preliminary results. *Adv. Exp. Med. Biol.* 2005; 566: 195-201.
23. Ito H, Kanno I, Iida H, et al. Arterial fraction of cerebral blood volume in humans measured by positron emission tomography. *Ann. Nucl. Med.* 2001; 15: 111-6.
24. Daubeney PE, Pilkington SN, Janke E, Charlton GA, Smith DC, Webber SA. Cerebral oxygenation measured by near-infrared spectroscopy: comparison with jugular bulb oximetry. *Ann. Thorac. Surg.* 1996; 61: 930-4.
25. Nagdyman N, Ewert P, Peters B, Miera O, Fleck T, Berger F. Comparison of

- different near-infrared spectroscopic cerebral oxygenation indices with central venous and jugular venous oxygenation saturation in children. *Paediatr. Anaesth.* 2008; 18: 160-6.
26. Ricci Z, Garisto C, Favia I, et al. Cerebral NIRS as a marker of superior vena cava oxygen saturation in neonates with congenital heart disease. *Paediatr. Anaesth.* 2010; 20: 1040-5.
27. Moerman A, Denys W, De Somer F, Wouters PF, De Hert SG. Influence of variations in systemic blood flow and pressure on cerebral and systemic oxygen saturation in cardiopulmonary bypass patients. *Br. J. Anaesth.* 2013; 111: 619-26.
28. Fogel MA, Li C, Wilson F, et al. Relationship of cerebral blood flow to aortic-to-pulmonary collateral/shunt flow in single ventricles. *Heart* 2015; 101: 1325-31.
29. Ter Minassian A, Poirier N, Pierrot M, et al. Correlation between cerebral oxygen saturation measured by near-infrared spectroscopy and jugular oxygen saturation in patients with severe closed head injury. *Anesthesiology* 1999; 91: 985-90.
30. Vranken NPA, Weerwind PW, Sutedia NA, Severdija EE, Barenbrug PJC, Maessen JG. Cerebral oximetry and autoregulation during cardiopulmonary bypass: a review. *J. Extra Corpor. Technol.* 2017; 49: 182-91.
31. Lewis SB, Myburgh JA, Thornton EL, Reilly PL. Cerebral oxygenation monitoring by near-infrared spectroscopy is not clinically useful in patients with severe closed-head injury: a comparison with jugular venous bulb oximetry. *Crit. Care Med.* 1996; 24: 1334-8.

**Tables**

Table 1. Cardiac pathologies in the study population

Diagnosis	Before surgery for double ventricles	After surgery for double ventricles	Before surgery for single ventricle	After surgery for single ventricle
Atrial septal defect	15	1		
Ventricular septal defect	37	16	1	
Atrioventricular septal defect	5	2	1	1
Aortic stenosis	3	3	1	1
Pulmonary atresia	1	1		
Patent ductus arteriosus	4			
Total anomalous pulmonary venous return		3		
Transposition of the great arteries	1	13	1	
Tetralogy of Fallot	2	14		
Double outlet right ventricle			1	
Single right ventricle			6	8
Single left ventricle			10	8
Others	4	6		
Total	72	66	21	18

Table 2. Demographic and physiological data from cardiac catheterization

	All children with				
	CHD (n=186)	Before surgery for double ventricle (n=72)	After surgery for double ventricle (n=66)	Before surgery for single ventricle (n=21)	After surgery for single ventricle (n=18)
Age, m	72.1 (84.5)	70.6 (67.1)	95.1 (96.8)	30.3 (42.1)	143.9 (90.9)
Sex, male:female	113:73	41:31	40:26	16:5	14:4
Height, cm	99.9 (35.5)	103.0 (38.0)	109.1 (33.3)	81.7 (24.8)	132.6 (30.4)
Weight, kg	19.7 (18.2)	22.0 (19.5)	23.6 (20.1)	11.4 (10.4)	33.8 (18.8)
rSO <sub>2</sub> , %	66 (13)	71 (13)	68 (13)	63 (11)	69 (14)
SjvO <sub>2</sub> , %	66 (10)	68 (9)	68 (9)	62 (8)	66 (8)
SaO <sub>2</sub> , %	93 (8)	95 (6)	95 (69)	81 (7)	91 (7)
Hb, g/dL	12.7 (6.6)	11.9 (1.6)	11.9 (1.9)	14.6 (2.6)	14.4 (2.6)
HR, bpm	98 (23)	93 (23)	90 (19)	107 (21)	85 (20)
sBP, mmHg	82 (12)	86 (10)	86 (13)	76 (10)	84 (10)
dBp, mmHg	45 (10)	45 (10)	49 (10)	38 (7)	49 (5)
Mean BP, mmHg	61 (10)	61 (9)	65 (11)	54 (7)	62 (5)
CVP, mmHg	9 (3)	7 (2)	9 (2)	11 (3)	14 (3)

Abbreviations: BP, blood pressure; CHD, congenital heart disease; CVP, central venous pressure; dBp, diastolic blood pressure; rSO<sub>2</sub>, regional oxygen saturation index; sBP, systolic blood pressure; SaO<sub>2</sub>, arterial Hb oxygen saturation; SjvO<sub>2</sub>, internal jugular venous Hb oxygen saturation

Table 3. Correlation of cerebral Hb oxygen saturation on NIRS with SjvO<sub>2</sub>, SaO<sub>2</sub>, and reference values of SO<sub>2</sub> under steady ratios of SjvO<sub>2</sub> and SaO<sub>2</sub> in double or single ventricle subgroups.

	rSO <sub>2</sub> vs SjvO <sub>2</sub>	rSO <sub>2</sub> vs SaO <sub>2</sub>	rSO <sub>2</sub> vs 0.75 × SjvO <sub>2</sub> + 0.25 × SaO <sub>2</sub>	rSO <sub>2</sub> vs 0.66 × SjvO <sub>2</sub> + 0.34 × SaO <sub>2</sub>	rSO <sub>2</sub> vs 0.5 × SjvO <sub>2</sub> + 0.5 × SaO <sub>2</sub>
All children with CHD (n=186)	0.483 <0.0001	0.252 0.001	0.505 <0.0001	0.500 <0.0001	0.486 <0.0001
Before surgery for double ventricle (n=72)	0.467 <0.0001	0.307 0.009	0.494 <0.0001	0.489 <0.0001	0.487 <0.0001
After surgery for double ventricle (n=66)	0.538 <0.0001	0.184 0.139	0.571 <0.0001	0.574 <0.0001	0.562 <0.0001
Before surgery for single ventricle (n=21)	0.539 0.010	0.611 0.003	0.632 0.002	0.643 0.001	0.662 0.001
After surgery for single ventricle (n=18)	0.141 0.576	-0.028 0.912	0.096 0.704	0.104 0.680	0.129 0.611

Abbreviations: CHD, congenital heart disease; NIRS, near-infrared spectroscopy; rSO<sub>2</sub>, regional oxygen saturation index; SaO<sub>2</sub>, arterial Hb oxygen saturation; SjvO<sub>2</sub>, internal jugular venous Hb oxygen saturation

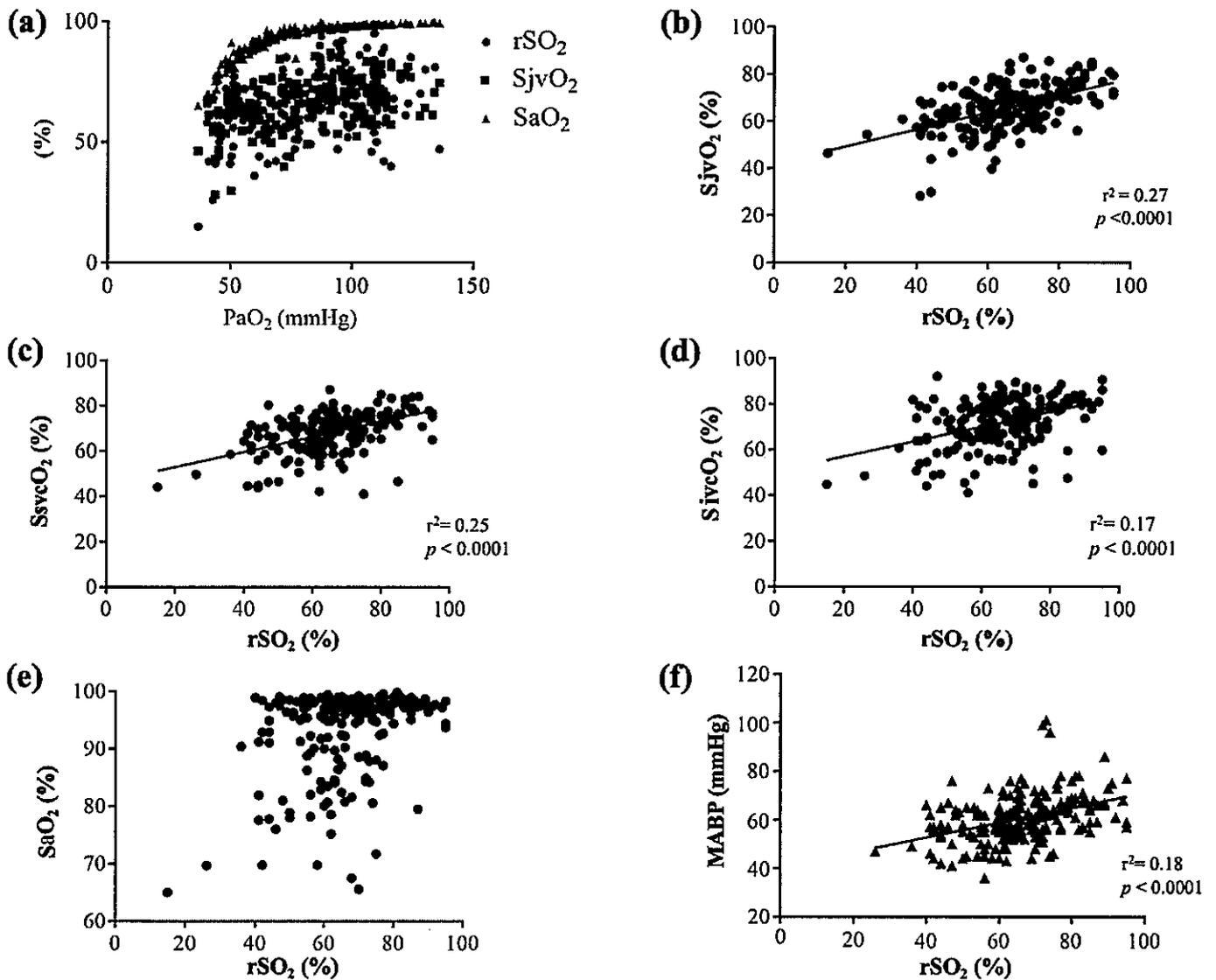
Table 4. Correlation of cerebral Hb oxygen saturation on NIRS with bHb, HR MABP, and CVP in double or single ventricle subgroups.

	rSO <sub>2</sub> vs bHb	rSO <sub>2</sub> vs HR	rSO <sub>2</sub> vs MABP	rSO <sub>2</sub> vs CVP
Before surgery of double ventricle (n=72)	0.3725	-0.4759	0.4815	0.1186
After surgery of double ventricle (n=66)	<0.0001	<0.0001	<0.0001	0.1327
Before surgery of single ventricle (n=21)	0.4701	-0.2781	0.5345	0.1545
After surgery of single ventricle (n=18)	<0.0001	0.0238	<0.0001	0.2155
	0.3068	-0.7251	0.3357	0.243
	0.1762	0.0002	0.1368	0.2884
	0.2261	-0.5459	-0.2488	-0.2886
	0.367	0.0191	0.3194	0.2454

Abbreviations: bHb, blood Hb concentration; CVP, central venous pressure; CHD, congenital heart disease; HR, heart rate; MABP, mean arterial blood pressure; NIRS, near-infrared spectroscopy; rSO<sub>2</sub>, regional oxygen saturation index

Table 5. Correlation of cerebral Hb oxygen saturation on NIRS with SjvO<sub>2</sub>, SaO<sub>2</sub>, and reference values of SO<sub>2</sub> under steady ratios of SjvO<sub>2</sub> and SaO<sub>2</sub> in subgroups with or without cyanosis.

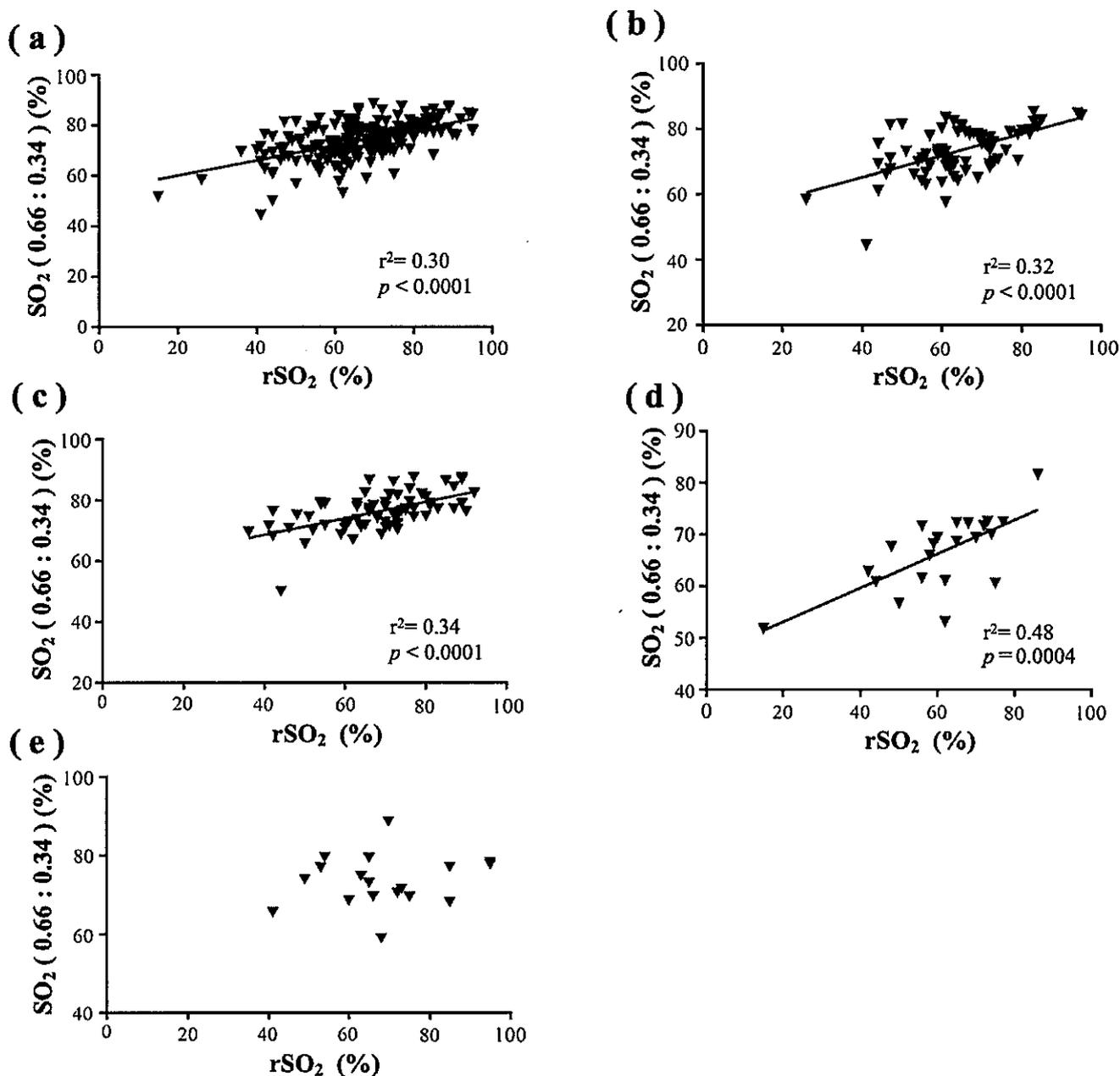
	rSO <sub>2</sub> vs SjvO <sub>2</sub>	rSO <sub>2</sub> vs SaO <sub>2</sub>	rSO <sub>2</sub> vs 0.75*SjvO <sub>2</sub> + 0.25*SaO <sub>2</sub>	rSO <sub>2</sub> vs 0.66*SjvO <sub>2</sub> + 0.34*SaO <sub>2</sub>	rSO <sub>2</sub> vs 0.5*SjvO <sub>2</sub> + 0.5*SaO <sub>2</sub>
Before surgery without cyanosis (n=75)	0.4508 <0.0001	0.1599 0.1707	0.4529 <0.0001	0.4351 <0.0001	0.4127 0.0002
After surgery without cyanosis (n=79)	0.439 <0.0001	0.1508 0.1845	0.4398 <0.0001	0.4497 <0.0001	0.4552 <0.0001
Before surgery with cyanosis (n=18)	0.3306 0.1803	0.3721 0.1284	0.4287 0.0759	0.3709 0.1297	0.4184 0.084
After surgery with cyanosis (n=5)	0.6 0.35	-0.4 0.5167	0.6 0.35	0.3 0.6833	0.3 0.6833



**Figure 1.**

Comparison of the relationship between  $rSO_2$  and Hb oxygen saturation in the internal jugular vein ( $SjvO_2$ ), superior vena cava ( $SsvcO_2$ ), inferior vena cava ( $SivcO_2$ ), femoral artery ( $SaO_2$ ), and mean arterial blood pressure (MABP) for all patients with CHD.

(a) Changes in  $SaO_2$ ,  $rSO_2$ ,  $SjO_2$ , and  $PaO_2$  in the artery. (b) Relationships between  $rSO_2$  and  $SjvO_2$ . (c) Relationships between  $rSO_2$  and  $SsvcO_2$ . (d) Relationships between  $rSO_2$  and  $SivcO_2$ . (e) Relationships between  $rSO_2$  and  $SaO_2$ . (f) Relationships between  $rSO_2$  and MABP.



**Figure 2.**

Relationships between  $rSO_2$  and the reference values of  $SO_2$  under steady ratios of  $SjvO_2$  and  $SaO_2$  in (a) all CHD patients and (b-e) the four subgroups. (b) Double ventricles before surgery. (c) Double ventricles after surgery. (d) Single ventricle before surgery. (e) Single ventricle after surgery. The reference values under steady  $SjvO_2:SaO_2$  ratios of 0.66:0.34 were calculated as  $SO_2$  (0.66:0.34) =  $0.66 \times SjvO_2 + 0.34 \times SaO_2$ .