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Chapter 8

APPLICABILITY OF NEAR-INFRARED SPECTROSCOPY (NIRS) IN CLINICAL NEONATOLOGY

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ABSTRACT

Near-infrared spectroscopy (NIRS) has been used for clinical research in newborn infants since 1985. It has contributed to the pathophysiological background knowledge of clinical neonatology, and the time might have come to put NIRS into clinical neonatal practice. This light-based approach is useful in the field because near-infrared light can reach the newborn brain owing to the thin scalp and skull. Although the widely used parameters of arterial oxygen saturation (SpO_2) and blood pressure are useful clinical signs, as well as the parameters for estimating the hemodynamics of newborn infants, they do not reflect the perfusion and delivery of oxygen to distant organs, particularly the brain. Spatially resolved spectroscopy can be used to assess cerebral hemoglobin (Hb) oxygen saturation and cerebral fractional tissue oxygen extraction (cFTOE) noninvasively. Furthermore, the newer technique of time-resolved spectroscopy can also measure the absolute values of Hb oxygen saturation and cerebral blood volume (CBV) at the same time. Since the major determinants of cerebral Hb oxygen saturation are changes in SpO_2, Hb levels, cerebral blood flow (CBF), and cerebral metabolic rate of oxygen utilization, a decrease in cerebral Hb oxygen saturation indicates hypoxia, ischemia, and congestion of blood in the brain. The decrease in cerebral Hb oxygen saturation with increased cFTOE reflects increased oxygen extraction by the brain as a compensatory mechanism for the decreased cerebral tissue oxygenation. Evaluation of these parameters may help clinicians in identifying newborn infants at risk, and prevent brain injury. The use of NIRS has been reported in newborn infants for detecting various conditions, including preoperative and intraoperative congenital heart disease and asphyxia, and in monitoring during and immediately after birth of preterm infants. Especially, extremely preterm infants are subject to a wide range of cardiopulmonary complications related to immature lung and cardiac function. Fluctuations in CBF with impaired cerebral autoregulation among these infants occasionally result in complication

in the form of periventricular-intraventricular hemorrhage (PIVH); therefore, assessment of the pattern of both cerebral Hb oxygen saturation and cFTOE may identify those infants at risk for severe PIVH.

INTRODUCTION

Drastic hemodynamic changes are observed in the adaptation from fetal to extrauterine life at birth. The fetal circulation consists of parallel circuits with predominant right ventricle output. The left ventricle becomes the sole supplier of systemic circulation after birth, and the work increases owing to the elevated systemic resistance caused by the removal of low-resistance placental circulation. Furthermore, the volume pumped by the left ventricle is fractionally increased by establishment of the pulmonary circulation and the shunt flow through the ductus arteriosus [1]. These specific environmental changes easily cause cardiac insufficiency and the development of cerebrovascular injuries such as cerebral hemorrhage and hypoxic-ischemic injury, due to the perturbation of cerebral hemodynamics in newborn infants soon after birth [2]. Neonatal pathophysiology has been increasingly understood, thanks to recent advances in medical technology, and this has resulted in a decrease in neonatal mortality, especially among preterm infants. However, there are concerns about the adverse neurodevelopmental outcome of survivors [3]. The typical hypoxic-ischemic injury in term infants is hypoxic-ischemic encephalopathy (HIE) due to asphyxia during the perinatal period. Periventricular leukomalacia (PVL) in preterm infants is associated with the presence of an arterial end zone (watershed area) in the periventricular white matter and disturbances in cerebral hemodynamics, particularly cerebral hypoperfusion due to decreased cerebral blood flow (CBF) [4]. Moreover, the risk factors for the development of periventricular-intraventricular hemorrhage (PIVH) in preterm infants are the presence of fragile immature capillaries in the germinal matrix and disturbances in cerebral hemodynamics, particularly cerebral hyperperfusion caused by increased CBF and/or increased venous and capillary pressures and hence increased cerebral blood volume (CBV), fluctuation of cerebral perfusion, and disturbed cerebral autoregulation [5-7]. Improving the ability to assess changes in cerebral oxygenation and regulation of CBF will enhance the understanding of how these changes may contribute to various forms of acquired brain injury, including HIE, PVL, and PIVH.

Continuous-wave near-infrared spectroscopy (NIRS) is a method used to measure cerebral oxygenation and hemodynamics. This method is noninvasive, continuous, and can also be used for bedside monitoring. However, its most important limitations are its inability to perform absolute quantitative measurements of oxygenation and hemodynamic parameters, and its sensitivity to movement artifacts; that is, with continuous-wave NIRS, only changes in the concentration of oxyhemoglobin (O_2Hb) and deoxyhemoglobin (HHb) can be measured, not the absolute level of these parameters [7]. Edwards et al. measured the CBF value first with NIRS in which Fick's principle was applied with oxygenated hemoglobin (Hb) as a tracer [8]. In this measurement method, the fraction of inspired oxygen is increased to induce a rapid elevation of arterial blood oxygen level, and the accompanying arterial blood Hb oxygen saturation is measured using a pulse oximeter; at the same time, the elevation of intracerebral oxygenated Hb level is measured by NIRS, and CBF is calculated. Moreover, CBF measurement with indocyanine green (ICG), instead of oxygenated Hb, has been

reported [9,10]. Roberts et al. applied this method for quantitative measurement during neonatal thoracotomy: changes in ICG level in exposed blood vessels and the head were simultaneously measured to evaluate CBF [11]. Kusaka et al. developed a method for the quantitative measurement of local CBF in which the cerebral ICG level is simultaneously measured by near-infrared topography, using pulse densitometry by applying the pulse oximeter principle for the determination of arterial blood ICG level [12]. However, these methods cannot be used for clinical monitoring because they provide one-shot static CBF. Additionally, these methods are also invasive because the indicators are radioactive and need to be injected intravenously.

Spatially resolved spectroscopy (SRS) is a variant of NIRS. The measurement depends on the determination of the ratio between the optical density at 2 or more distances from the emitter. The cerebral Hb oxygen saturation [= O_2Hb / (O_2Hb + HHb)] on an absolute scale can be monitored continuously with this method. The commercially available devices give this ratio different names: tissue oxygenation index (TOI) in NIRO (Hamamatsu Photonics, Hamamatsu City, Japan) and regional oxygen saturation (rSO_2) in INVOS (Somanetics, Troy, MI, USA). However, the methods used are different. TOI is calculated using the diffusion equation, whereas rSO_2 is calculated using a different formula where scattering is measured at the first optode (at 2 cm) and deducted from the measurements at 4 cm. With the INVOS near-infrared spectrometer, a transducer containing a light-emitting diode and 2 distant sensors are attached to the fronto-parietal side of the neonatal skull. The concept of Hb oxygen saturation measured by NIRS is based on the assumption that the cephalic region is composed of homogenous tissue [13]. Both cerebral TOI (cTOI) and cerebral rSO_2 ($rScO_2$) measured in the fronto-temporal region reflect the saturation of oxygen in the veins (70–80%), capillaries (5%), and arteries (20–25%) of the brain [14]. It has been compared and used as a surrogate measure of the oxygen saturation in jugular venous blood (SvO_2). However, jugular SvO_2 measures pure venous blood, whereas cTOI and $rScO_2$ measure a mixed venous saturation. Clinically, cTOI and $rScO_2$ reflects the changes in SpO_2, blood flow, blood volume, and oxygen consumption. To investigate the balance between oxygen delivery and oxygen consumption, relative fractional tissue oxygen extraction [FTOE = (SpO_2 - TOI or rSO_2) / SpO_2] measurement can be performed. Naulaers et al. showed a close correlation between the FTOE measured by NIRS and the actual fractional oxygen extraction (FOE) in piglets, and concluded that FTOE is likely to provide important information on the oxygenation status of the brain continuously; FTOE represents the ratio of oxygen uptake to oxygen delivery [15]. An increase in cerebral FTOE (cFTOE) might indicate a reduced delivery with a constant oxygen consumption of the brain or a higher consumption than oxygen delivery. The opposite is true in the case of a decrease in cFTOE, reflecting a decrease of oxygen extraction due to less utilization of oxygen or constant oxygen consumption with an increased oxygen delivery.

The recently developed method of time-resolved spectroscopy (TRS) enables the assessment of quantitative hemodynamics, absolute values of cerebral Hb oxygen saturation (cSO_2) and CBV measured by absolute values of O_2Hb and HHb [16]. This method has the advantage of being able to perform measurements in different infants at different times, and to compare each result. Moreover, this device enables the simultaneous quantitative analysis of μ_a and light-reduced scattering coefficient ($\mu's$) in tissue by using the photon diffusion

theory. The μ′s is a new parameter for the assessment of structural changes in the brain, such as brain edema and myelination.

This chapter reviews the mean values of NIRS parameters, the pathophysiological background knowledge for neonatology, and the clinical value of NIRS in the critical management of newborn infants.

MEAN VALUES OF NIRS PARAMETERS

1. Hb Oxygen Saturation and FTOE

Clinically, the cerebral Hb oxygen saturation value reflects the changes in SpO_2, blood flow, blood volume, and oxygen consumption. Although there are several different commercial instruments that use several different wavelengths, and each instrument measures Hb oxygen saturation, 2 of them are most popular in the neonatal field: TOI in NIRO (Hamamatsu Photonics) and rSO_2 in INVOS (Somanetics). A recent study showed that the mean cerebral Hb oxygen saturation is similar between NIRO 200 NX and INVOS 5100, whereas that of NIRO 300 was significantly lower [17]; that is, there are differences between different commercial devices. In addition, the parameter reflects differences in clinical care procedures after birth [18], gestational age (GA) or birth weight (BW) [19], region of the brain [20], and sleeping position [18].

Some studies reported cTOI, $rScO_2$, and cFTOE values for term and preterm infants in the first day of life. The cTOI values reported widely ranged from 57.0% to 74.7% by using NIRO 300 [21-24]. Sorensen and Greisen showed that cTOI (74.7 ± 13.9%) in healthy term infants (n = 25, GA: 39.7 ± 1.3 weeks, BW: 3484 ± 346 g) were significantly lower than that (78.6 ± 15.2%) in preterm infants (n = 46, GA: 29.1 ± 2.6 weeks, BW: 1307 ± 437 g), and cFTOE was higher in term infants (0.22 ± 0.66) than in preterm infants (0.18 ± 0.07) on the first day of life (median age: 19.2 h) using NIRO 300 [23].

Ijichi et al. reported an absolute cSO_2 value of 70.0 ± 4.6% (mean ± SD) as determined by a TRS system (Hamamatsu Photonics) in 22 neonates (GA: 36.8 ± 3.1 weeks, BW: 2365 ± 791 g) [16]. We also evaluated the mean values of cSO_2, both in term infants (n = 32, GA: 38.9 weeks, BW: 2980 ± 334 g) and preterm infants (n = 40, GA: 32.5 weeks, BW: 1722 ± 408 g) within 72 h of birth by using a TRS-20 and showed that the mean cSO_2 values were approximately 70% in both groups [25]. Moreover, in a study of both extremely low birth weight (ELBW: BW <1000 g) infants (n = 22, GA: 25.2 ± 2.0 weeks, BW: 683.0 ± 175.6 g) and very low birth weight (VLBW: 1000 < BW < 1500 g) infants (n = 25, GA: 28.5 ± 1.4 weeks, BW: 1298.0 ± 151.6 g) during 72 h after birth, the mean cSO_2 values were also approximately 70% [26]. Although the cerebral Hb oxygen saturation level, cTOI and $rScO_2$, differs depending on the commercial instrument used, the typical values range from 65% to 85% in newborn infants. The typical values of cFTOE with these commercial instruments are also within 0.2–0.4.

2. Mean CBV Value

The estimated CBV values in neonates were 2.22 ± 0.4 and 3.7 mL/100 g by using the modified Beer-Lambert law, with changes in arterial saturation [27] and PCO_2 [27], respectively. Leung et al. reported an estimated CBV of 1.72 ± 0.76 mL/100 g as determined by SRS with ICG [29]. Ijichi et al. reported an absolute CBV of 2.31 ± 0.56 mL/100 g as determined by a TRS system in 22 neonates of GA >30 weeks (GA: 36.8 ± 3.1 weeks, BW: 2365 ± 791 g), and indicated that CBV increases with postconceptional age, owing to the percentage of blood vessel area in the gray matter and white matter, both of which increase as a function of GA [16].

It has been reported that the CBV in human adults was 4.81 ± 0.37 mL/100 g, as measured by single-photon emission computed tomography [30], and 4.7 ± 1.1 mL/100 g by using positron emission tomography [31]; both values were higher than those in neonates.

Our recent study showed absolute CBV values of 2.06 ± 0.40 mL/100 g in term infants (n = 32, GA: 38.9 weeks, BW: 2980 ± 334 g) and 1.67 ± 0.28 mL/100 g in preterm infants (n = 40, GA: 32.5 weeks, BW: 1722 ± 408 g), using a TRS-20 within 72 h after birth [16]. In our study of VLBW infants, however, the CBV in the ELBW group of BW <1000 g (n = 22, GA; 25.2 ± 2.0 weeks, BW; 683.0 ± 175.6 g) was significantly higher than in the VLBW group of BW 1000 g < BW < 1500 g (n = 25, GA; 28.5 ± 1.4 weeks, BW; 1268.0 ± 151.6 g) within 72 h after birth (2.50 ± 0.58 mL/100 g vs. 1.83 ± 0.46 mL/100 g, $P < 0.01$) (Figure 1) [8]. The typical value of CBV is 1.5–2.5 mL/100 g in newborn infants.

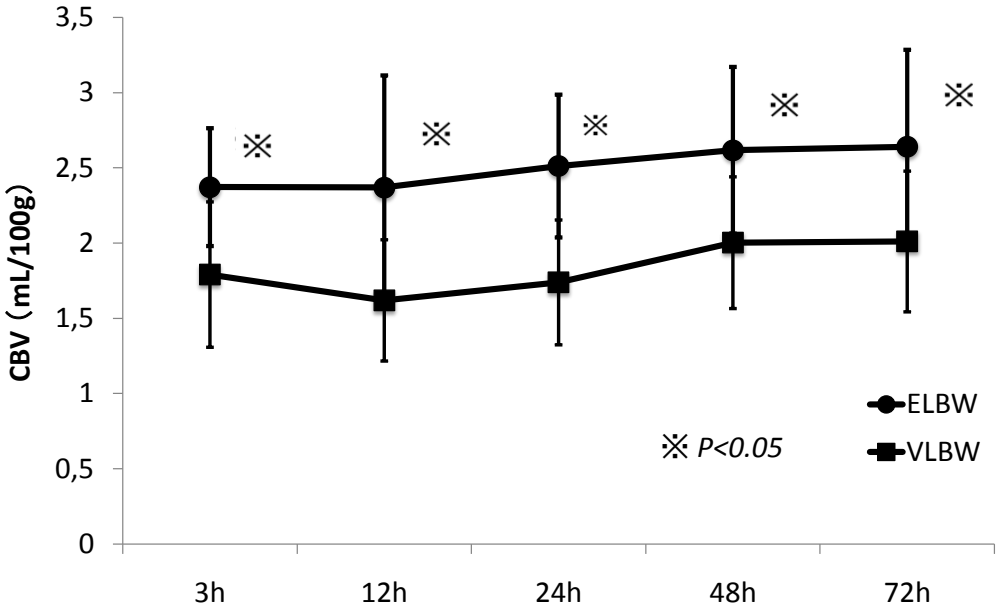

Figure 1. Longitudinal changes in cerebral blood volume (CBV) in both the extremely low birth weight (ELBW) group and the very low birth weight (VLBW) group. The CBV in the ELBW group (birth weight < 1000 g) was significantly higher than in the VLBW group (1000 g < birth weight < 1500 g) within 72 h after birth (2.50 ± 0.58 mL/100 g vs. 1.83 ± 0.46 mL/100 g, $P < 0.01$). ●, ELBW group; ■, VLBW group.

PATHOPHYSIOLOGICAL BACKGROUND KNOWLEDGE FOR NEONATOLOGY

1. Time Course Changes in NIRS Parameters

Several reports have shown significant changes in cerebral Hb oxygen saturation for term and preterm infants after birth. Urlesberger et al. evaluated $rScO_2$ and cFTOE in term infants (n = 61, GA: 39 ± 1 weeks, BW: 3439 ± 411 g) immediately after birth, using INVOS 5100, and found that $rScO_2$ increased from 44% (3 min) to 76% (7 min), and cFTOE decreased about from 4.0 (3 min) to 2.0 (5 min), but it did not change significantly after 5 min [32]. Noori et al. showed that $rScO_2$ increased from 47% at 1 min to 83% at 8 min, then decreased progressively to 73% at 20 min in 20 neonates (GA: 39.1 ± 1.3 weeks, BW: 3449 ± 392 g) [33]. We evaluated the time course changes in cTOI and cFTOE in 27 healthy term infants (GA: 38.3 ± 1.3 weeks, BW: 2927 ± 322 g) at 3–6, 12, 24, 48, and 72 h after birth by using NIRO 300 [24]. cTOI showed a relatively low value at 3–6 h after birth (58.0 ± 3.6%), and then significantly increased until 24 h (62.1 ± 3.0%) and gradually decreased until 72 h (61.7 ± 4.0%) (Figure 2). cFTOE showed a relatively high value at 3–6 h (0.41 ± 0.03), and then decreased significantly until 24 h (0.36 ± 0.03) and gradually increased until 48 h after birth (0.37 ± 0.04).

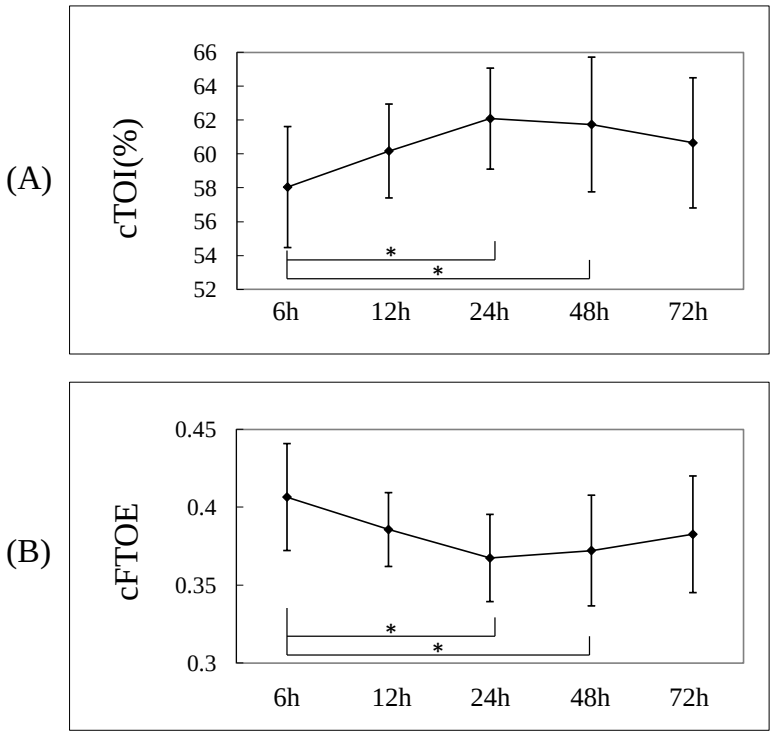

Figure 2. Longitudinal changes in cerebral tissue oxygenation index (cTOI) (A) and cerebral fractional tissue oxygen extraction (cFTOE) (B) in 27 healthy term newborn infants. cTOI showed a relatively low value at 6 h after birth and then gradually increased until 24 h. The cTOI at 6 h after birth significantly decreased at 24 and 48 h. The cFTOE showed a relatively high value at 6 h after birth and then gradually decreased until 24 and 48 h. *$P < 0.05$.

Naulaers et al. showed that cTOI increased significantly in the first 3 days of life in preterm infants (n = 15, GA: 28.0 weeks), using NIRO 300: 57% on day 1, 66.1% on day 2, and 76.1% on day 3 [21]. Concerning cTOI in extremely preterm infants during the first 72 h after birth in our study (n = 16, GA: 25.2 ± 1.6 weeks, BW: 749 ± 252 g), the value of 65.4% at 3–6 h decreased to 57.6% at 12 h, and showed trends of gradual increase from 18 to 72 h (67.8%) after birth [22]. cFTOE increased from 3 to 6 h (0.31) after birth to 12 h (0.36), and then decreased after 18 h (0.28 at 72 h).

2. Chronological Changes in Preterm Infants

Our recent study evaluated chronological changes in cSO_2, cFTOE, CBV, and μ′s in 29 preterm infants (n = 29, GA: 27.3 ± 1.9 weeks, BW: 1041 ± 309 g) from the first day after birth to the corrected GA (cGA) by using TRS-20 [34]. Significant negative correlations were observed between postconceptional age and cSO_2 or Hb levels. Conversely, positive correlations were observed between postconceptional age and cFTOE or μ′s. The μ′s at the cGA was significantly lower in preterm infants than in term infants. We propose that the decrease in cSO_2 and increase in cFTOE with the cGA is attributable to increased cerebral oxygen extraction to compensate for the advancing anemia. The increase in μ′s after cGA might indicate developmental changes in the brains of preterm infants. A lower μ′s at cGA in preterm infants compared with that in term infants may be indicative of an immature brain.

3. Appropriate for GA and Small for GA Infants

Being small for GA (SGA) and intrauterine growth restriction are associated with an increase in perinatal mortality. These conditions, associated with chronic fetal hypoxia and undernutrition due to placental insufficiency, result in hemodynamic adaptation that allows preferential redistribution of blood flow to the brain; this is called the “brain sparing effect” [35]. However, whether this phenomenon indicates either a higher risk of brain injury or a protective mechanism remains uncertain [36].

We evaluated cSO_2, CBV, and cFTOE by using TRS-20 during the immediate postnatal period in 57 appropriate for GA (AGA) infants (GA: 33.8 ± 4.5 weeks, BW: 2126.2 ± 789.9 g) and 30 SGA infants (GA: 35.2 ± 2.7 weeks, BW: 1687.6 ± 423.1 g) without significant differences in GA and head circumference [37]. We also evaluated the left ventricular ejection fraction (LVEF) and left ventricular cardiac output (LVCO), as the parameters of systemic perfusion, using echocardiography. Although CBV showed no significant difference between the groups, cSO_2 was significantly higher and cFTOE was lower in SGA infants than in AGA infants. Hematocrit (Ht) levels were significantly higher, and LVEF and LVCO were lower, in SGA infants than in AGA infants. A negative correlation was observed between CBV and Ht levels in AGA infants but not in SGA infants. The high Ht levels and vasoreactivity in SGA infants might be a compensatory mechanism to maintain oxygen delivery to the brain, which reflects the condition of chronic hypoxia during the fetal period and also reflects the weak contraction and low cardiac output of the left ventricle, sustaining the relatively large brain from the fetal period to after birth.

4. Effects in Cases of Significant Patent Ductus Arteriosus

Incomplete closure of the ductus arteriosus is frequently seen in about 35% of preterm infants, especially extremely preterm infants, after treatment with a surfactant for respiratory distress syndrome. Hypoperfusion of vital organs with a ductal steal (left-to-right shunt) phenomenon, and finally myocardial dysfunction due to left-sided volume overload, can cause PIVH, necrotizing enterocolitis, or renal failure [38]. A serious patent ductus arteriosus (PDA), which leads to cardiac failure, is associated with these important morbidities; however, it is unclear whether the association between PDA and these morbidities is a result of the left-to-right PDA shunt itself, the therapies used for treatment, or the immaturity of the infant who is likely to develop a PDA. A recent report showed that sudden changes in systemic perfusion treated with surgical ligation increased the risk of alteration in cerebral perfusion compared with indomethacin treatment [39]. This means that the timing of starting indomethacin treatment should be known, before PDA patients develop severe complications.

We evaluated the changes in cerebral and systemic circulation in preterm infants (n = 14, GA: 27.3 ± 2.0 weeks, BW: 989.6 ± 235.2 g) who showed a significant PDA to investigate the effects of the PDA shunt itself [40]. cSO_2, CBV, and cFTOE, measured using TRS-20, as well as the left ventricular end-diastolic dimension (LVDd), left atrium to aorta ratio (LA/Ao), LVCO, and superior vena cava (SVC) flow, using echocardiography, as parameters of "echocardiographically significant PDA" were evaluated before indomethacin treatment and also after PDA closure. SVC flow is considered an echocardiographic parameter that can evaluate cerebral perfusion [22]. The mean arterial blood pressure (MABP) increased, but LVDd, LA/Ao, and LVCO decreased significantly after the indomethacin treatment. However, there were no significant differences in cSO_2, CBV, cFTOE, and SVC flow values before and after treatment. These results may demonstrate that the left-to-right shunt itself in echocardiographically significant PDA appears to affect the systemic circulation but not the cerebral circulation. We think that evaluation of echocardiographic parameters might help in preventing severe PDA patients from developing severe complications.

5. Effects of Umbilical Cord Milking in Preterm Infants

A recent Cochrane Review demonstrated that infants who had delayed cord clamping were less likely to require red blood cell transfusion for low blood pressure and had a lower incidence of PIVH after birth [41]. Hosono et al. showed in a recent randomized controlled study that umbilical cord milking facilitated the early stabilization of both blood pressure and urine output, and reduced the need for both red blood cell transfusion and circulatory and respiratory support in VLBW infants [42,43]. We hypothesized that umbilical cord milking may have similar effects to delayed cord clamping in preterm infants in terms of initial Hb values and the reduced need for red blood cell transfusions, as well as reduced PIVH risk.

We evaluated cTOI and cFTOE in 50 stable VLBW infants by using NIRO 300 at 3–6, 12, 18, 24, 36, 48, and 72 h after birth; the infants were divided into 2 groups: those who had umbilical cord milking (milked group; n = 26, GA; 25.8 ± 1.6 weeks, BW; 849 ± 218 g) and those who did not (control group; n = 24, GA; 25.1 ± 2.1 weeks, BW; 851 ± 221 g) [44]. LVDd, LVEF, left ventricular Tei index, LVCO, and SVC flow were measured concurrently with echocardiography. Ht, LVDd, LVCO, and SVC flow were higher in the milked group

than in the control group, with improvement in the left ventricular Tei index within 24 h after birth. cTOI increased and cFTOE decreased in the milked group within 24 h after birth. We concluded that umbilical cord milking stabilized cerebral oxygenation and perfusion in preterm infants by improving left ventricle diastolic function through increased left ventricle preload.

6. Anemic Preterm Infants and Transfusion

Preterm infants have a high risk of becoming rapidly anemic owing to both frequent laboratory blood sampling and their immature hematopoietic system. Approximately 80% of extremely preterm infants will receive at least one blood transfusion by the end of the hospitalization period. The most widely used criteria for determining the need for neonatal transfusion are based on the levels of blood Hb and Ht; however, clinically useful indicators of physiologically significant anemia requiring transfusions of red blood cells have yet to be defined in preterm infants [45]. A recent study demonstrated that blood transfusion improved cerebral oxygenation, and a simultaneous decrease in cFTOE served as a compensatory mechanism [46]. Koyano et al. showed that transfusion decreased CBV and increased cSO_2 in anemic preterm infants, and changes in CBV were greater when the Hb levels were low before transfusion [47]. They also suggested that measurement of CBV in anemic patients might be a useful variable for assessing cerebral hemodynamic conditions. Evaluation of both CBV and cSO_2 may be useful criteria for determining the need for transfusion, in addition to the levels of Hb or Ht, in clinical neonatology.

CLINICAL NEONATAL PRACTICE

1. Evaluation Before, During, and After Congenital Cardiac Surgery

Investigations with NIRS have increased in the field of pediatric cardiology, with a growing understanding of the risks for perioperative brain injury. Several studies have evaluated cerebral oxygenation among infants with congenital heart diseases (CHDs) in the intraoperative, and in both preoperative and postoperative settings in infants undergoing cardiac surgery. The information gathered from these studies may help guide interventions by the surgical term or intensive care physicians to maintain theoretically safe cerebral oxygenation levels. As an intraoperative monitoring, some studies evaluated the association of NIRS findings with direct clinical outcomes. Fenton et al. demonstrated that patients (n = 34) who died after a single ventricle first-stage palliation had lower $rScO_2$ at the end of the operation (P = 0.01), but with no correlation to clinical neurologic abnormalities [48]. McQuillen et al. demonstrated that decreased $rScO_2$ during aortic cross-clamping in patients (n = 16) was associated with abnormal postoperative magnetic resonance imaging (MRI) (P = 0.08) [49]. Dent et al. found that prolonged low postoperative $rScO_2$ <45% for more than 180 min was associated with either new or worsening lesions on postoperative MRI (P = 0.029) [50]. On the other hand, de Vries et al. found that $rScO_2$ decreases with balloon inflation in

patients (n = 11) with intracardiac shunts, and that the recovery time is directly related to inflation time [51].

We evaluated cTOI in preoperative hypoxic gas management of CHD with increased pulmonary blood flow in order to find the safe SpO_2 levels. An example infant (GA: 39 weeks, BW: 2942 g) with coarctation of the aorta with ventricular septal defect (VSD) controlled by ventilation is shown in Figure 3.

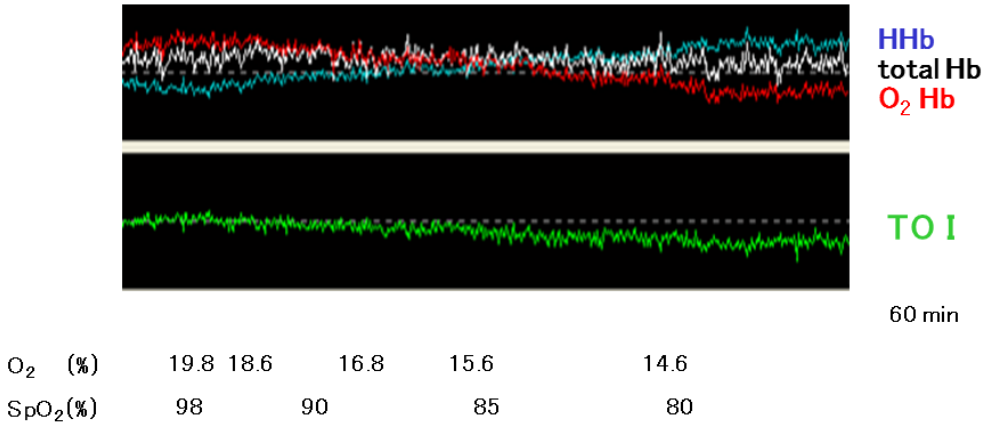

Figure 3. An example infant (gestational age: 39 weeks, birth weight: 2942 g) with coarctation of the aorta with ventricular septal defect (VSD) controlled by ventilation. A nitrogen gas mixture was administered, with a target oxygen saturation (SpO_2) of 80%. The fractional inspired oxygen concentration (FiO_2) decreased from 0.21% (room air) to 14.6% in 60 min. Oxyhemoglobin (O_2Hb) decreased and deoxyhemoglobin (HHb) increased gradually. The cerebral tissue oxygenation index (cTOI) also decreased from 66% to 55%.

The patient received hypoxic gas management on the eighth day after birth to decrease pulmonary blood flow. A nitrogen gas mixture was administered, and SpO_2 in the right upper arm and cTOI was measured, continuously targeting an SpO_2 of 80%. The fractional inspired oxygen concentration (FiO_2) decreased from 0.21% (room air) to 14.6% in 60 min, and the cTOI decreased from 66% to 55%. A total of 8 infants (GA: 36 ± 3 weeks, BW: 2537 ± 576 g) with CHD with increased pulmonary blood flow were evaluated for cTOI and peripheral TOI (on the right brachial artery) during hypoxic gas management [52]. There were 3 infants with 2 functional ventricles, including coarctation of the aorta with VSD, truncus arteriosus communis, and interruption of the aortic arch (type A). A single functional ventricle was observed in the other 5 infants: 3 had hypoplastic left heart syndrome and the other 2 had tricuspid atresia (type Ic).

The SpO_2 before the initiation of hypoxia was 97.0 ± 2.1%, and the minimum SpO_2 after initiation of hypoxia was 80.8 ± 2.9%, and the change in SpO_2 was –16.3 ± 3.2%, when the minimum FiO_2 was 16.2 ± 1.1%. With a decrease in SpO_2 after the initiation of hypoxia, cTOI decreased to 57.6 ± 7.7% and peripheral TOI decreased to 57.4 ± 4.8%. When the hypoxic gas was discontinued, SpO_2 increased, and both cerebral and peripheral TOI recovered to their baseline value in all infants. We concluded that a safer control of SpO_2 should maintain the value at >80% for hypoxia management in infants with CHD because the change in cerebral TOI was ≦10% when SpO_2 was ≧80%. NIRS monitoring in patients with

CHD in the intraoperative, and in both preoperative and postoperative settings of infants undergoing cardiac surgery may be useful for understanding the risks for perioperative brain injury.

2. Evaluation in Infants with Asphyxia

HIE in infants with asphyxia remains a major cause of permanent neurodevelopmental disability and infant mortality, occurring in about 1 to 2 babies per 1000 term live births. Amplitude integrated electroencephalography (aEEG) is increasingly being used in the neonatal intensive care unit as a continuous monitor of brain function. The background pattern during the first 3 h of life has a high positive predictive value for an adverse outcome; the device is therefore useful to select infants with HIE eligible for induced hypothermia treatment, as soon as possible, at the bedside [53]. Previous studies reported that changes in cerebral oxygenation in newborns with HIE were strictly related to the severity of brain injury. Kusaka et al. reported that the cSO_2 values of asphyxiated infants were higher or lower than those in normal term infants within 58–72 h of birth [54]. Toet et al. showed that a pattern of increased rSO_2 and decreased cFTOE 24 h after birth in newborn infants with perinatal asphyxia was associated with an adverse outcome [55].

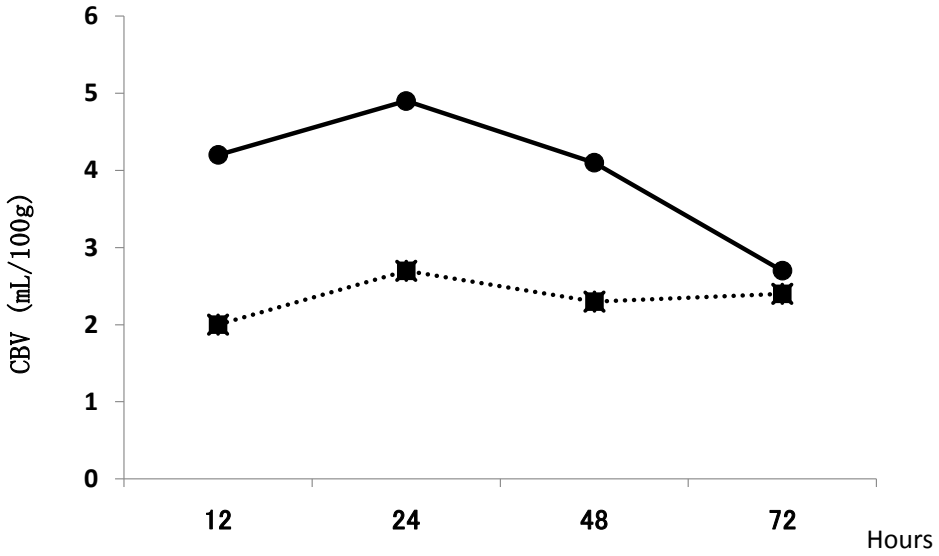

Figure 4. An example of an infant with asphyxia (gestational age: 39 weeks, birth weight: 4040 g) with an adverse outcome [59]. The cerebral hemoglobin oxygen saturation (cSO_2) level was increased at 48 h after birth, whereas cerebral blood volume (CBV) measured by TRS-20 was significantly increased at 6 h after birth. This indicated that CBV might be more sensitive than cSO_2 in evaluating newborn infants with neonatal asphyxia. Dotted line showed the changes of CBV in healthy term infants.

This result is in agreement with the concept of secondary energy failure and luxury reperfusion after a severe ischemic insult. Another group has reported that increases in CBV and CBF were observed in infants with asphyxia within 48 and 24 h of birth, respectively [56,57]. Furthermore, a recent animal study, using a newborn piglet model, demonstrated that

combining CBV with aEEG may be a more effective guide to control hypoxic-ischemic insults than aEEG alone [58]. Figure 4 shows an example of 1 infant with asphyxia (GA: 39 weeks, BW: 4040 g) with an adverse outcome [59]. The Apgar scores were 0, 1, and 3 at 1, 5, and 10 min, respectively. The cSO_2 level was increased at 48 h after birth, whereas CBV measured by TRS-20 was significantly increased at 6 h after birth. This indicated that CBV might be more sensitive than cSO_2 for the evaluation of newborn infants with neonatal asphyxia. Some recent reports showed that the aEEG pattern during hypothermic treatment was changed by the effect of this therapy [60,61].

Moreover, Ancora et al. evaluated 12 asphyxiated newborns undergoing brain cooling management and showed that only 4 of them developed an adverse outcome among 10 newborns who showed an abnormal background pattern on aEEG at 24 h of life, whereas infants who developed an adverse outcome showed a high TOI level at 6, 12, and 24 h of life on the NIRO 200 [62]. The combined evaluation of cSO_2 and CBV is expected to contribute to the understanding of hypoxic-ischemic insults, from the perspectives of cerebral circulation and cerebral function, indicated by aEEG. They could be used as reliable prognostic indicators of asphyxia in infants who could be treated with induced hypothermia.

3. Management in Preterm Infants

1) Cerebral Autoregulation in Preterm Infants

Autoregulation is the property of the arteries to constrict in response to an increase in transmural pressure, and to dilate in response to a decrease in pressure, with the effect of keeping blood flow more or less constant within a range of arterial blood pressures [63]. This response has a limited capacity, and, as a result, blood flow will decrease when blood pressure decreases below a lower threshold and increase when blood pressure increases above an upper threshold. In these circumstances, CBF has a direct linear relation with MABP. Failure of cerebral autoregulation combined with hypotension has been implicated in the pathogenesis of both ischemic and hemorrhagic cerebral lesions. As it is not possible in routine clinical practice to determine CBF directly, it has become standard practice to maintain the MABP during cerebral hypoperfusion [64]. In the management of premature infants, it is believed that the MABP should not be allowed to decrease to <30 mm Hg in sick infants and/or it is recommend to maintain the MABP above the value of an infant's GA in weeks, although there is little evidence to support this protocol [65].

By using NIRO 500, Tyszczuk et al. [64] and Munro et al. [66] showed that CBF is independent of MABP over a wide pressure range in preterm infants, and this suggests that autoregulation may actually be effective in the immature brain. On the other hand, Soul et al. indicated that autoregulation may be absent not only in sick preterm infants but also in those who are clinically well [67].

Flora et al. evaluated the relation between MABP and cTOI in very preterm infants (n = 24, GA; 28 ± 22 weeks) at a mean postnatal age of 28 (±22) h, using NIRO 300. They demonstrated that impaired autoregulation, signified by a high coherence between MABP and cTOI, was present in a subgroup of clinically sick infants and was strongly associated with subsequent mortality [68]. They concluded that SRS (NIRO 300) has the potential to provide continuous assessment of cerebral autoregulation at the bedside, and, hence, this approach may guide therapeutic interventions in critically ill infants.

2) Cerebral Circulation and Systemic Circulation

We demonstrated that even in stable condition, extremely preterm infants have reduced cerebral oxygenation and perfusion immediately after birth, which likely result from low cardiac output due to decreased left ventricular contractility and increased peripheral vascular resistance [22]. If a sick, extremely preterm infant showed a low level of cTOI on continuous monitoring NIRS, an intervention such as volume expansion followed by an infusion of inotropic drugs should be considered.

In the clinical setting, a decrease in cTOI indicates hypoxia, ischemia, or congestion of blood in the brain owing to cardiac failure. Stabilizing cardiac function and cardiac output might stabilize both the cerebral circulation and the systemic circulation [44]. Greisen et al. proposed that the cerebral oxygenation target range be 55–85%, as a clinical management point in extremely preterm infants [69].

3) Cerebral Circulation and Blood Pressure

It is generally accepted in clinical neonatology that hypotension is defined as an MABP value below an infant's GA in weeks [65]. Although the blood pressure values are useful clinical signs, as well as other parameters for estimating the hemodynamics of newborn infants, the relation between MABP and the perfusion or delivery of oxygen to distant organs such as the brain is not well known.

We evaluated the relations of MABP, cSO_2, and CBV with time in 18 extremely preterm infants within 72 h after birth [70]. The subjects were divided into 2 groups: those who showed hypotension at least once during the study period (LBP group, n = 8, GA: 24.9 ± 0.4 weeks, BW: 663.6 ± 66.0 g) and those who did not (NBP group, n = 8, GA: 24.7 ± 0.5 weeks, BW: 699.2 ± 70.7 g). cSO_2 and CBV were measured at 3, 12, 24, 48, and 72 h after birth by using TRS-20. MABP was significantly lower in the LBP group than in the NBP group at 3 and 24 h after birth. Although there was no significant difference in CBV between the LBP group and the NBP group, a significant difference between the 2 groups was observed in cSO_2 at 24 h after birth. Our study showed that systemic hypotension is associated with low cerebral oxygenation in preterm infants. On the other hand, Figure 5 shows a contrasting example in an extremely preterm infant who did not have a low cerebral oxygenation level even when showing a low MABP value.

The longitudinal changes in MABP and cSO_2 within 72 h after birth from this example are shown. The infant was under morphine sedation from soon after birth, and infusion of dobutamine, dopamine, and hydrocortisone was administered to treat the low MABP. Grade III PIVH was diagnosed by cranial ultrasound at 66 h after birth. We suspected that this bleeding in the brain was caused by reperfusion (i.e., hyperperfusion due to increased CBF), by using infusion of dobutamine, dopamine, and hydrocortisone after low MABP. In this case, the levels of cSO_2 were within the normal range (70–85%), whereas the MABP values were low during the study period; the MABP did not reflect the cerebral oxygenation in this instance.

We assert that even though low systemic blood pressure is generally associated with deoxygenation in the brain, ScO_2 should be evaluated in each infant to determine the appropriate brain-centered treatment in neonatal medical care.

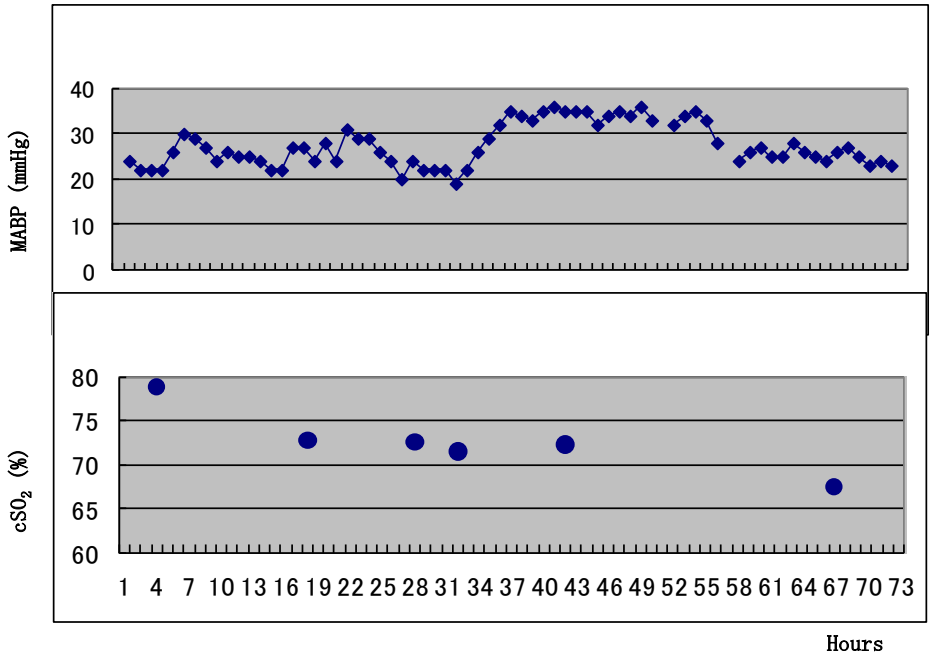

Figure 5. Longitudinal changes in the mean arterial blood pressure (MABP) and cSO_2 within 72 h after birth in the example infant who was complicated with grade III periventricular-intraventricular hemorrhage. The levels of cSO_2 were within the normal range (70–85%) when the infant showed low MABP during the study period. HC, hydrocortisone; DOA, dopamine; DOB, dobutamine.

4) Cerebral Circulation and PIVH

PIVH is known to occur in extremely preterm infants and is attributable to multiple pathogenetic factors, including the vulnerability of the vasculature and fragility of the germinal matrix of the brain. Hypotension and hypoperfusion of the brain during the immediate postnatal period have been reported to be related to cerebral damage in sick preterm infants. Kluckow and Evans proposed Doppler echocardiographic measurement of blood flow in the SVC as a consistent marker of upper body perfusion, including CBF [71]. They reported that the proportion of sick preterm infants who developed PIVH was related to the period of hypoperfusion and reperfusion within the first 48 h of life [72]. We evaluated the relation between low cTOI and PIVH in 51 preterm infants (GA: 27.0 ± 1.9 weeks, BW: 967.3 ± 250.0 g) by using NIRO 300 within 72 h after birth [73]. Low levels of cTOI (<55%) were observed in 8 infants and PIVH (>grade II) was observed in 4 infants. All 4 infants who had complicated IVH showed low cTOI during the study period. A cutoff value of 55% for the low level in the TOI target range had 100% sensitivity and 93% specificity for detecting PIVH. In contrast to our studies, Alderliesten et al. recently suggested an association between hyperperfusion and severe PIVH (>grade III) in a case-control study [74]. They concluded that higher $rScO_2$ and lower cFTOE values measured by INVOS 4100/5100 suggest increased perfusion before the development of severe PIVH. Infants with severe PIVH received more inotropic drugs before the diagnosis of PIVH. These conditions, as reflected in both the $rScO_2$ and cFTOE values, might represent the reperfusion period in the brain. The necessity of aggressive medication should be assessed when sick infants show low MABP within the target range of $rScO_2$, since reperfusion might consequently follow hypoperfusion.

CONCLUSION

The near-infrared light-based approach is useful in newborn infants because near-infrared light can reach the newborn brain owing to the thin scalp and skull. Cerebral Hb oxygen saturation, that is, TOI and rSO_2, measured by SRS noninvasively, and cFTOE are useful parameters in evaluating the oxygenation and metabolism in the brain. cTOI and $rScO_2$ are changes in SpO_2, Hb levels, CBF, and cerebral metabolic rate of oxygen utilization; therefore, a decrease in these parameters indicates hypoxia, ischemia, and congestion of blood in the brain in the clinical setting. The decrease in cTOI/$rScO_2$ with increased cFTOE reflects increased oxygen extraction by the brain as a compensatory mechanism for the decreased cerebral tissue oxygenation. The typical range of cTOI/$rScO_2$ values is from 65% to 85% in newborn infants, whereas that of cFTOE is 0.2–0.4. The newly developed TRS method enables to evaluate the absolute values of both cSO_2 and CBV at the same time. The range of the mean CBV value in infants might be from 1.5 to 2.5 mL/100 g.

NIRS has contributed to the pathophysiological background knowledge of cerebral oxygenation, perfusion, and metabolism, including the time course changes in both term and preterm infants, chronological changes in preterm infants, differences between AGA and SGA infants, the effects in cases of significant PDA, the effects of umbilical cord milking in preterm infants, and the evaluation in anemic preterm infants. The evaluation of NIRS parameters may help clinicians in identifying newborn infants at risk, and prevent brain injury. The use of NIRS has been reported in newborn infants for various conditions, including preoperative and intraoperative CHD, asphyxia, and monitoring immediately after birth. The time might have come to put NIRS into clinical neonatal practice.

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