岩手医科大学
審査学位論文
（博　士）

JIMA Vol. 66, No. 2 (June 2014) pp. 57-65.

Original

Cerebral, renal and muscular tissue oxygenation indices in preterm infants

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(Received on December 3, 2013 & Accepted on January 14, 2014)

Abstract

Reference values for tissue oxygenation index (TOI) of various organs in low birth weight (LBW) infants during the first 24 h of life have not been determined. In preterm LBW infants (mean gestational age, 33 weeks; mean birth weight, 1970 g) without mechanical ventilation, administration of inotropic agents, or symptomatic patent ductus arteriosus, we simultaneously measured TOI of the brain, gut, right kidney, and quadriceps muscle using near-infrared spectroscopy at 1-2, 3, 6, 12, and 24 h after birth. Superior vena cava flow, left ventricular output (LVO) and resistance index of the anterior cerebral, celiac, superior mesenteric and renal arteries were measured with ultrasonography. Correlations and factors related to TOI were analyzed. Mean TOI during the first 24 h of life was 70-76% in the brain, 69-73% in the right kidney, and 77-80% in the quadriceps muscle. No significant difference was seen in comparisons by either measurement time or site, despite significant changes in hemodynamic variables during the study period. Reliable data were not obtained for the gut because of large fluctuations. Cerebral and renal TOI correlated significantly with LVO at 24 h. Cerebral, renal and muscular TOI were maintained until 24 h after birth in healthy, stable preterm infants.

Key words : near-infrared spectroscopy, tissue oxygenation index, resistance index, left ventricular output, preterm infants

I. Introduction

Spatially resolved spectroscopy, one of the measurement principles of near-infrared spectroscopy (NIRS), enables the calculation of tissue oxygenation index (TOI) from measurements of the relative concentrations of oxygenated hemoglobin (O_2Hb) and deoxygenated hemoglobin (HHb). TOI expresses tissue oxygen saturation as an absolute value according to the formula $TOI = O_2Hb/(O_2Hb+HHb)$, and enables comparison of tissue oxygenation between subjects[1]. Most NIRS studies of preterm low birth weight (LBW) infants have been conducted for a short period in sick infants requiring cardiorespiratory support, and baseline data from healthy, stable preterm infants are limited[2-12]. Although a recent study in stable preterm infants during the first week of life showed daily changes in regional oxygen saturation (rSO_2) derived using a different NIRS technique

and algorithm[13], significant disagreement is seen between TOI and rSO_2 values[14]. The present study conducted serial simultaneous measurements of TOI in the brain, gut, kidney, and quadriceps muscle during the first 24 h of life in healthy, stable preterm LBW infants without mechanical ventilation, administration of inotropic agents, or symptomatic patent ductus arteriosus (PDA) to elucidate natural changes in TOI.

II. Materials and methods

1. Subjects

We enrolled infants weighing 1000-2499 g born in our hospital and admitted to the neonatal intensive care unit from March 1, 2011 to April 30, 2012. Infants meeting the following criteria during hospitalization were excluded: 1) presence of chromosomal abnormality or major congenital malformation; 2) small for gestational age; 3) resuscitation by bag and mask or intubation at birth; 4) oxygen administration of $FIO_2 > 0.25$ or mechanical ventilation; 5) use of inotropic agents; 6) symptomatic PDA; 7) plethora (hematocrit ≥ 65%); 8) severe anemia (hematocrit < 35%); or 9) sepsis (either positive blood culture, Ig M ≥ 20 mg/dl at birth, or use of intravenous immunoglobulin). This study was approved by the ethics committee of our university and written consent was obtained from the parents of all subjects prior to enrollment. Subjects were managed according to standard practices.

2. Measurement of heart rate, blood pressure, and oxygen saturation

Heart rate was measured using an electrocardiograph (IntelliVue MP70 Neonatal; Phillips Healthcare Japan, Tokyo, Japan), and mean blood pressure (MBP) was measured with an indirect oscillometric method (BX-10; Colin, Tokyo, Japan). Transcutaneous oxygen saturation (SpO_2) was measured using a pulse oximeter (Radical; Masimo, Irvine, CA, USA) attached to the right arm or leg after confirming that there was no difference between the two sites. These recordings were made in combination with NIRS as described below for 30 min at 1-2 h after birth and for 20 min at all other measurement times. Heart rate and SpO_2 data were automatically saved on a personal computer once every 30 s, and MBP was saved once every 30 min at 1-2 h and every 20 min at 3, 6, 12 and 24 h after birth. In the analyses of heart rate and SpO_2, mean values at each measurement time were used.

3. TOI measurement

TOI was measured simultaneously in the brain, gut, right kidney, and quadriceps muscle using NIRS (NIRO 200 NX; Hamamatsu Photonics, Hamamatsu, Japan). Probe attachment sites were the forehead for the brain, above the umbilicus for the gut, the right flank with confirmation by ultrasound for the right kidney, and the left inner thigh for the quadriceps muscle. Probes were attached using double-sided tape. Measurements were made once every 2 s for 30 min at 1-2 h, and for 20 min at 3, 6, 12, and 24 h after birth. Results were automatically saved to a personal computer and mean values of measurements were used for analyses.

4. Measurement of blood flow volume and resistance index

Superior vena cava (SVC) flow, left ventricular output (LVO) and resistance index (RI) of the anterior cerebral artery

(ACA), celiac artery (CA), superior mesenteric artery (SMA) and renal artery (RA) were measured using ultrasonography (iE33; Philips Healthcare, Bothell, WA, USA) and a 12-MHz probe. SVC flow and LVO were calculated following the reports of Kluckow et al.[15] and Alverson et al.[16], respectively. RI was calculated following the method described by Bada et al.[17]

5. Evaluation of patent ductus arteriosus

The ductus arteriosus was observed using color Doppler ultrasonography at the time of the above blood flow measurements, and cases were judged patent when continuous shunt blood flow was seen from the aorta to the main pulmonary artery.

6. Statistical analysis

Analysis of variance with Tukey correction was performed for intragroup comparisons according to time after birth for each type of data. The *t*-test was used for intergroup comparisons by site. Pearson's correlation coefficient was obtained for SVC flow and LVO data. To analyze factors related to TOI, multiple regression analysis was performed with TOI at each measurement time as the dependent variable, and gestational age (GA), birth weight, mode of delivery, heart rate, MBP, SpO_2, SVC flow, LVO and RI at each measurement time as independent variables. Statistical analyses were performed using SPSS for Windows (SPSS Japan, Tokyo, Japan), with values of $p<0.05$ (two-sided) considered significant. Data are expressed as mean ± SD unless otherwise indicated.

III. Results

1. Subject characteristics (Table 1)

Eighty-four preterm infants weighing 1000-2499 g were admitted to our hospital during the study period, and the exclusion criteria applied to 64. Of the remaining 20, measurements could not be made for the second infant of 3 pairs of twins, because only one NIRS machine was available, and could not be made in 2 infants because no examiner was present. As a result, subjects comprised 15 infants (8 boys, 7 girls). GA of the subjects was 33 ± 2 weeks (range, 30-35 weeks) and birth weight was 1970 ± 338 g (range, 1428-2424 g). Thirteen of the 15 subjects were diagnosed with having transient tachypnea of the newborn or apnea of prematurity, and oxygen was administered ($FIO_2 \leq 0.25$) in the incubator within 24 h after birth. Subcutaneous hemorrhage of the head was seen because of NIRS attachment in 1 case. No apnea attacks occurred during measurements and no subjects started enteral nutrition

Table 1. Characteristics of the subjects

Variable	Value
Gestational week	33.3 (1.9)
Birth weight (g)	1970 (337.8)
Male / female	8/7
Mode of delivery	
Vaginal delivery	3 (20%)
Caesarean section	12 (80%)
Apgar score	
≦ 7 (1 min)	5 (33%)
≦ 7 (5 min)	0
O_2 supplementation	13 (86%)
SEH	1 (7%)
PVL	0
CLD	0

Values indicate mean (SD) or number (%).
SEH, subependymal hemorrhage; PVL, periventricular leukomalacia; CLD, chronic lung disease.

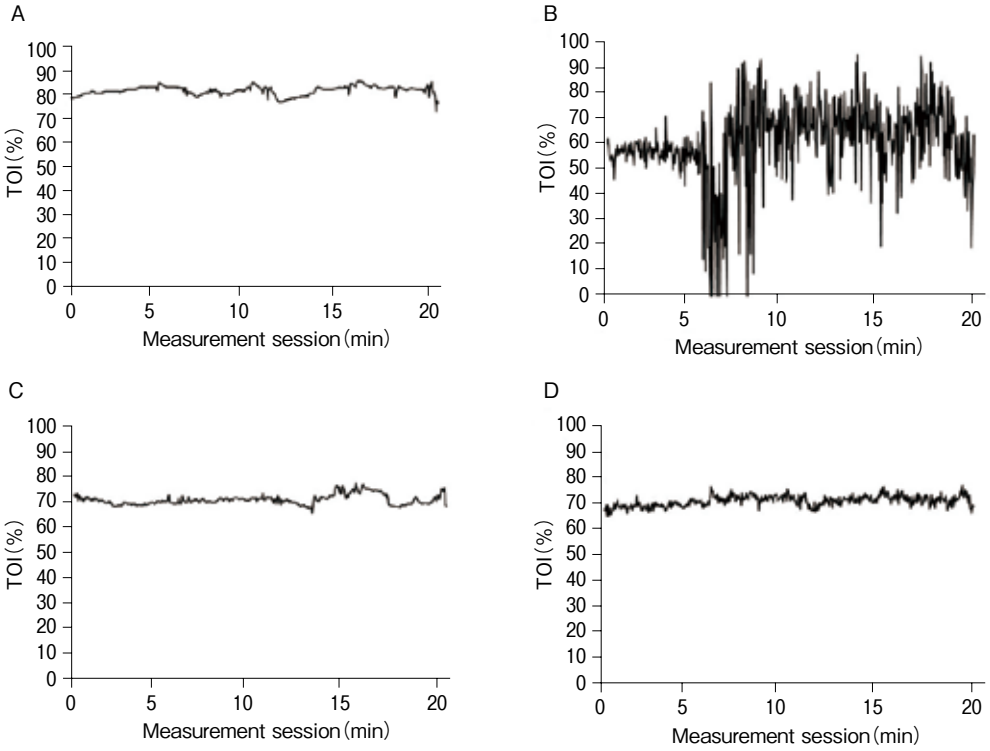

Fig. 2. Changes of TOI of a patient
A, TOI of brain; B, TOI of gut; C, TOI of right kidney; D, TOI of quadriceps muscle.

within 24 h. Subependymal hemorrhage was seen on echoencephalography in 1 patient after the study, but no cases of periventricular leukomalacia were seen on brain computed tomography or magnetic resonance imaging at the time of discharge.

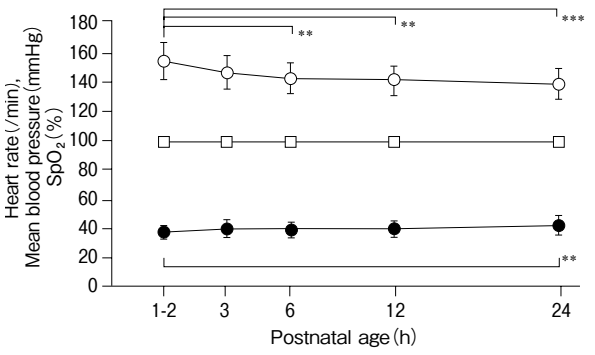

Fig.1. Serial changes of heart rate, mean blood pressure, and SpO_2
○, heart rate; ●, mean blood pressure; □, SpO_2. ** $p<0.01$, *** $p<0.001$.

2. Changes in heart rate, MBP, and SpO_2 over time (Fig. 1)

Heart rate decreased from 155 ± 13/min at 1-2 h to 143 ± 11/min at 6 h ($p=0.006$), 141 ± 10/min at 12 h ($p=0.002$), and 139 ± 10/min at 24 h ($p<0.001$). MBP elevated from 37 ± 5 mmHg at 1-2 h to 42 ± 7 mmHg at 24 h ($p=0.024$). SpO_2 did not show any significant changes up to 24 h.

3. Changes in TOI over time

Figure 2 shows TOI in a representative case. Mean SDs for TOI of the brain, right kidney, and quadriceps muscle were 3.7% (95% confidence interval (CI), 3.3-4.1%) for the brain, 3.1% (95%CI, 2.6-3.5%) for the right kidney, and 3.8% (95%CI, 3.3-4.3%) for the quadriceps muscle, showing very little change. Individual TOI of the gut, however, varied greatly from 0% to 100% and error

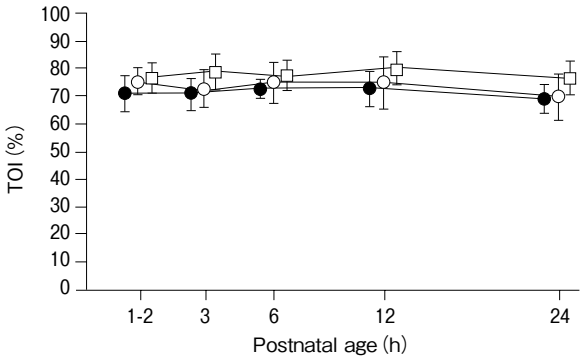

Fig. 3. Serial changes of mean TOI
○, TOI of brain; ●, TOI of right kidney; □,TOI of quadriceps muscle.

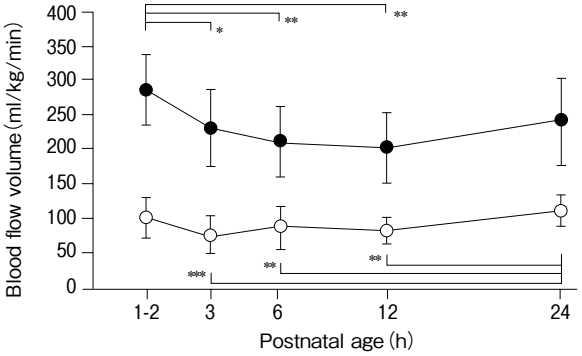

Fig. 4. Serial changes of blood flow volume of major vessels
○, superior vena cava flow; ●, left ventricular cardiac output. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

displays were frequent. Reliable data were thus not obtained (Fig. 2B).

The range of mean TOI (Fig. 3) up to 24 h after birth was 70-76% for the brain, 69-73% for the right kidney, and 77-80% for the quadriceps muscle. No significant differences were seen in comparisons by either measurement time or site.

4. Changes in blood flow volume and RI over time

SVC flow was 101 ± 23 ml/kg/min at 1-2 h, 77 ± 27 ml/kg/min at 3 h, 85 ± 30 ml/kg/min at 6 h, and 8 ± 19 ml/kg/min at 12 h, and was significantly increased to 111 ± 23 ml/kg/min at 24 h compared with 3 h ($p<0.001$), 6 h ($p=0.007$) and 12 h ($p=0.002$) (Fig. 4). LVO decreased from 288 ± 52 ml/kg/min at 1-2 h to 227 ± 57 ml/kg/min at 3 h ($p=0.039$), 211 ± 51 ml/kg/min at 6 h ($p=0.003$), and 205 ± 54 ml/kg/min at 12 h ($p=0.001$) (Fig. 4). Correlation analysis showed a significant correlation between SVC flow and LVO at 24 h after birth ($r=0.534$, $p=0.040$).

The RI of the ACA was 0.8 ± 0.1 at 1-2 h and 3 h, 0.7 ± 0.1 at 6 h and 0.8 ± 0.1 at 12 h, and significantly decreased to 0.7 ± 0.1 at 24 h compared with 1-2 h ($p<0.001$) and 3 h ($p=0.027$). RI of the CA was 0.9 ± 0.1 at 1-2 h, 0.8 ± 0.1 at 3 h, and decreased significantly to 0.7 ± 0.1 at 6 h and 12 h ($p<0.001$, respectively) and 0.7 ± 0.0 at 24 h ($p<0.001$) compared with 1-2 h. RI of the SMA was 0.9 ± 0.0 at 1-2 h and 0.9 ± 0.1 at 3 h, and decreased to 0.8 ± 0.1 at 6 h ($p<0.001$), 0.8 ± 0.1 at 12 h ($p=0.001$) and 0.8 ± 0.1 at 24 h ($p=0.024$) compared with 1-2 h. RI of the RA was 0.9 ± 0.1 at 1-2 h, 3 h, 6 h and 12 h, and decreased significantly to 0.8 ± 0.1 at 24 h compared with 1-2 h ($p<0.001$) and 3 h ($p=0.005$).

5. Analysis of factors related to TOI

According to multiple regression analysis, TOI of the brain and right kidney appeared significantly related to LVO at 24 h after birth (brain: $r=0.593$, $p=0.033$; right kidney: $r=0.669$, $p=0.009$; quadriceps muscle: $r=0.528$, $p=0.053$).

6. Changes in ductus arteriosus over time

PDA was seen in 15 infants at 1-2 h and 3 h, 14 infants at 6 h, 10 infants at 12 h, and

7 infants at 24 h. Cases of patency were significantly decreased at 24 h compared with 1-2 h ($p<0.001$), 3 h ($p<0.001$), and 6 h ($p=0.003$). Symptomatic PDA was not observed in any study patients.

IV. Discussion

In healthy, stable preterm LBW infants without mechanical ventilation, use of inotropic agents or symptomatic PDA, TOI was serially measured at 4 sites, including pre- and post-ductal organs. The results showed TOI was maintained despite significant changes in circulatory variables including indices of blood flow volume and vascular resistance up to 24 h after birth. In a multiple regression analysis, TOI of the brain and right kidney showed a significant correlation with LVO at 24 h after birth.

Since studies of NIRS in preterm infants have mainly investigated TOI in the brain in sick infants who required cardiorespiratory support, reference values have yet to be established[2-8]. In preterm infants, Naulaers et al.[2] found that cerebral TOI (median and 95%CI) in infants of GA 25-30 weeks and birth weight 1053 ± 395 g (n=15) was 57.0% (54.0-65.7%) within 6 h of age and 66.1% (61.9-82.2%) at 24 h of age. Moran et al.[4] reported a mean cerebral TOI of 68.1 ± 7.9% in measurements at 8-23 h of age in neonates with GA 25-31 weeks and birth weight 570-1489 g (n=27). Sorensen et al.[5] reported that cerebral TOI (mean and 95%CI) at 18.9 ± 5.8 h of age in neonates with GA 29 ± 3 weeks and birth weight 1307 ± 436 g (n=46) was 78.6% (76.9-80.3%). Takami et al.[6] reported a significant decrease in mean cerebral TOI from 3-6 h (data not shown) to 57.6 ± 6.9% at 12 h of age in neonates of GA 23-28 weeks and birth weight 551-998 g (n=16), with a gradual increase thereafter. These reports included infants who needed cardiorespiratory support, developed symptomatic PDA or intraventricular hemorrhage, or died, so cerebral autoregulation and perfusion might have been impaired in some patients[8]. In contrast, cerebral TOI of term infants without any complications was reported by Sorensen et al.[5] as 74.7% (95%CI, 72.3-77.1%, n=25) at 20.2 ± 6.3 h after birth. Suganami et al.[7] reported a mean value of 58.0 ± 3.6% (n=27) at 6 h after birth and a significant increase to 62.1 ± 3.0% at 24 h after birth.

We have found no reports of muscular TOI in preterm infants[3,9-12]. Muscular TOI in term infants with (n=33) or without (n=33) positive results for C-reactive protein was reported by Pichler et al.[11] as 68.9 ± 6.6% and 72.9 ± 3.8% ($p=0.008$), respectively, at 41 h after birth. Tax et al.[12] reported that muscular TOI in asphyxiated term infants (umbilical artery pH ≦ 7.15 and Apgar score ≦ 6 at 5 min, n=8) was significantly lower compared to controls (n=30; 67.7 ± 5.5% vs. 71.8 ± 4.9%, $p=0.045$). TOI values in the present study were similar to values reported for normal term infants.

To the best of our knowledge, renal TOI has not been reported. McNeill et al.[13] studied cerebral and renal rSO_2 in 12 stable preterm infants (GA 29-30 weeks, n=6; GA 32-33 weeks, n=6) and reported cerebral rSO_2 as 66-83% and renal rSO_2 as 64-87% during the first 21 days of life. No significant difference in either value was seen between the two GA groups. The rSO_2 value has been shown to be significantly higher than the TOI value,

so comparison of these results to the present findings is difficult[14].

This study aimed to elucidate natural changes in TOI among healthy, stable preterm LBW infants. As a result, mean SDs of TOI in the brain, right kidney, and quadriceps muscle were all around the 3% level, and the range was narrower than in the above reports.

In this study, gut TOI varied greatly from 0% to 100% and error displays were frequent, so no reliable data could be obtained. Both TOI and rSO_2 values for the gut have been found to be considerably lower than at other sites, by 25-71% (n=32)[18] and 21.0-78.1% (n=38)[19], and the range of fluctuation is larger. When there are effects from scattering of near-infrared light by bowel gas and intestinal peristalsis, extremely low measurement values are shown and the fluctuation range is increased, so tissue oxygen saturation measurements may not be accurate. Two methods of attaching probes for the measurement of gut TOI have been used, above or below the umbilicus. If probes are attached above the umbilicus, the stomach and liver would interfere with measurements. Conversely, the bladder and the urine within it would interfere with probes under the umbilicus. In this study, probes were attached above the umbilicus, and interference from stomach gas and the liver might have contributed to the difficulty with measurements.

Serial changes in LVO were the same as previously described[20]. In multiple regression analysis, TOI of the brain and right kidney was significantly related to LVO at 24 h after birth. This is thought to express the fact that cases of ductus arteriosus closure increase significantly around this time, resulting in blood being effectively pumped to the entire body from the left ventricle. The significant elevation in MBP at 24 h after birth may also be explained by ductus closure. In contrast, even though MBP, blood flow volume and regional vascular resistance changed until 24 h after birth, no significant difference in mean TOI was evident in comparisons by either time or site. These results indicate the presence of autoregulation of vital (brain) and non-vital (kidney and muscle) organ perfusion in this population[8].

Conventional respiratory and circulatory management of LBW infants depends on monitoring of SpO_2, transcutaneous partial pressure of oxygen, heart rate, and blood pressure, along with echocardiography, but has not reached a level where it is useful in preventing periventricular leukomalacia, acute kidney injury, necrotizing enterocolitis, or retinopathy of prematurity arising from tissue hypoxia, ischemia, or oxygen toxicity. New indicators for cardiorespiratory management are therefore needed, and monitoring by NIRS appears promising. In this study, subjects comprised a group with little heterogeneity, and values obtained may prove helpful for determining reference values for LBW infants with characteristic conditions or complications in the future. However, the study population was limited and a larger study is necessary to establish normal values for TOI.

Conflict of interest: The authors have no conflict of interest to declare.

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岩手医誌 66 巻，2 号（平成 26 年 6 月）57-65 頁.

近赤外分光法による低出生体重児の経時的組織酸素飽和度測定

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(Received on December 3, 2013 & Accepted on January 14, 2014)

要旨

人工呼吸器や循環作動薬を必要としない早産児 15 例（在胎 33 週 ± 2 週，出生体重 1,970 ± 338g，平均 ± SD）を対象に，近赤外分光法により脳，消化管，右腎，大腿四頭筋の組織酸素化指標（tissue oxygen index，TOI）を生後 1 ～ 2，3，6，12，24 時間に測定した．同時に心拍数，平均血圧，SpO_2 と，超音波検査により上大静脈血流量と左室拍出量を測定し，TOI との関連について検討した．この結果，生後 24 時間までの平均 TOI は，脳が 70 ～ 76 %，右腎が 69 ～ 73%，大腿四頭筋が 77 ～ 80%で推移し，それぞれの生後時間別比較と部位別比較ともに有意差を認めなかった．消化管は変動が大きく，信頼できるデータは得られなかった．生後 24 時間に，脳と右腎の TOI と左室拍出量は有意な関連を示した．

人工呼吸器や循環作動薬を必要としない早産低出生体重児では，生後の循環動態が変化する時期でも TOI は一定に維持された．