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Evaluation of changes in cerebral perfusion in healthy term newborn infants during the immediate postnatal period

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Abstract

The time course of changes in cerebral perfusion in healthy term newborn infants during the early postnatal period is not fully understood. The tissue oxygenation index (TOI) and fractional tissue oxygen extraction {FTOE=(SpO_2 − TOI)/SpO_2} in cerebral perfusion were measured in 27 healthy term newborn infants using near-infrared spectroscopy (NIRS) at 6, 12, 24, 48, and 72 hrs after birth. The superior vena cava (SVC) flow and resistance index of the anterior cerebral artery (RI-ACA) were also measured using ultrasonography. The TOI and SVC flow, which are parameters of cerebral oxygenation and upper body perfusion, showed a relatively low value at 6 hrs after birth and then gradually increased, showing a peak value at 24 hrs. The RI-ACA and FTOE, which represents the ratio of oxygen extraction in cerebral tissue, showed a relatively high value at 6 hrs after birth and then gradually increased until 24 hrs after birth. A significant positive correlation was observed between TOI and SVC flow. The mean arterial blood pressure (MABP) gradually increased after birth. However there were no significant correlations between MABP and other parameters. Decreases of both cerebral tissue oxygenation and blood flow were observed in healthy term newborn infants immediately after birth. These changes might be affected by the cerebral edema caused by stress at birth and the changes in systemic perfusion with the adaptation of the circulatory system from fetal to extrauterin life. The measurements of TOI and FTOE using NIRS, and SVC flow using echocardiography might be useful parameters for noninvasive assessment of cerebral perfusion in neonates.

Introduction

Drastic hemodynamic changes are observed in 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 by the elevated systemic resistance caused by removal of low-resistance placenta circulation. Furthermore, the volume that the left ventricular pumps is fractionally increased by establishing pulmonary circulation and the shunt flow through the ductus arteriosus[1]. In addition, newborn infants face difficult conditions of mechanical stress through the birth canal. These specific environmental changes easily cause cardiac insufficiency, hypoxic-ischemic encephalopathy (HIE), and intraventricular hemorrhage (IVH) in newborn infants soon after birth[2].

Neonatal pathophysiology has been increasingly understood thanks to recent medical technology. However the changes in cerebral and systemic perfusion during the immediate postnatal period are not fully understood. The aim of this study is to characterize in detail the relationship between cerebral oxygenation and oxygen extraction using near infrared spectroscopy (NIRS), and systemic blood flow using echocardiography in healthy

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term newborns during the early postnatal period.

Methods

Subjects

Healthy term newborn infants (2,500 g≤ birth weight <4,000 g, 37 weeks ≤ gestational age <42 weeks), who were born in our university hospital between June 1, 2008 and December 31, 2008, were included in this study. Infants with congenital anomalies or those who were small for gestational age (birth weight < the 10th percentile for gestational age) were excluded. Infants who developed respiratory disorder or jaundice during the study period were also excluded. Informed consent was obtained from the parents of all infants. The study was approved by the Research Ethics Committee of Tokyo Medical University.

NIRS measurement

The oxygenated Hb (O_2Hb), deoxygenated Hb (HHb), and total Hb (cHb=O_2Hb+HHb) levels were measured using NIRS (NIRO-300 ; Hamamatsu Photonics KK, Shizuoka, Japan). The optode was placed in the front-temporal region of the head with the sensors at 30 mm distance and the wavelength at 120 nm[3]. Measurements were taken 6, 12, 24, 48, and 72 hrs after birth, and each measurement session lasted for 15 min. The results were recorded and stored as graphs and numerical values in a personal computer. The tissue-oxygenation index (TOI) was calculated from the O_2Hb and total Hb (O_2Hb/cHb×100). The cerebral fractional tissue oxygen extraction (FTOE) was then calculated from the TOI and oxygen saturation (SpO_2) values [FTOE=(SpO_2 − TOI)/SpO_2][4].

Echocardiographic measurement

All scans were performed using iE33 equipped with a 12 MHz transducer (Phillips Healthcare, Japan). The congenital heart disease was diagnosed using two-dimensional echocardiographic examination based on a segmental approach and excluded from the subjects[5)6)]. The patent ductus arteriosus was diagnosed with continuous mosaic image in ductus arteriosus by color Doppler echocardiography[7]. SVC flow was measured by the method of Kluckow et al[8]. Briefly, the SVC was imaged entering the right atrium (RA) from the parasternal long axis view, and then the maximum and minimum internal diameters were measured from the M mode tracing through the SVC at the level of which it enters the RA. The SVC was imaged entering the RA from the subcostal view, and then the pulsed Doppler recording was made at the junction of the SVC and the RA. The SVC flow pattern was pulsatile with two peaks ; ventricular systole and early ventricular diastole. The mean velocity of blood flow was calculated from the integral Doppler velocity tracings and was averaged from 3 consecutive cardiac cycles. The SVC flow was calculated using the following formula : SVC flow=(velocity time integral×(π×(mean SVC diameter^2/4)×HR)/body weight (ml/kg/min).

Cranial Doppler sonography measurement

All scans were performed using iE33 equipped with a 12 MHz transducer (Phillips Healthcare, Tokyo Japan). The anterior cerebral artery (ACA) was assessed via the anterior fontanelle by the tranceducer in the midsagittal plane and then shown by color Doppler image. The waveforms of ACA by pulse Doppler image were recorded for analysis of peak systolic velocity (Vs) and maximum end-diastolic velocity (Vd). The resistance index (RI) was calculated using the following formula : RI=((Vs − Vd)/Vs)[9]. The RI of ACA (RI-ACA) was averaged from 3 consecutive cardiac cycles.

Measurement of other variables

The mean arterial blood pressure (MABP) was measured by an oscillometric technique with an inflatable cuff (BSN-2303 ; Nihon Kohden Corporation, Tokyo, Japan) in all subjects. The heart rate (HR) and the SpO_2 in the right upper arm were continuously measured using a pulse oximeter (Nellcor Pulse Oximeter N-200 ; Tyco Healthcare Japan, Tokyo, Japan). The HR and SpO_2 were monitored and recorded every 30 seconds by a neonatal monitoring system (BSM-2300 ; Nihon Kohden Corporation). The data were stored in a personal computer, and median values were calculated over the measurement period.

All measurement ; NIRS, echocardiography, cranial Doppler sonography, and other variables were performed by a single examiner (YS).

Statistics

Statistical analyses were performed using the computer package SPSS for Windows (SPSS Japan, Tokyo, Japan). The gestational age, birth weight, and blood pH of the 27 infants were expressed as means±SD. Serial data obtained using NIRS, echocardiography, and physical examination at different time points were compared using repeated-measures ANOVA, followed by Bonferroni's multiple comparison tests. Pearson's correlation coefficients and simple linear regression analysis were used to determine the relationships among the MABP, SVC flow, RI-ACA, TOI and FTOE. $p<0.05$ was considered statistically significant.

Results

A total of 31 infants in healthy term newborn infants were included in the study. Four infants were excluded from this study because of insufficiency of the data. This means that a total of 27 infants became the subjects of the study. The mode of delivery, gender, gestational age, birth weight and Apgar score were shown in Table 1. The ductus arteiosus in all subjects was constricted completely within 24 hrs after birth.

Table 1 Clinical data of 27 healthy term newborn infants. The ductus arteriosus of all the subjects were closed by 24 hrs after birth.

Variable	Value (mean [SD])/# cases
Gestational age (weeks)	38.3 [1.3]
Birth weight (grams)	2927 [322]
vaginal/cesarean	16/11
male/female	11/16
Apgar score (1)	8.5 [0.8]
(5)	9.6 [0.5]

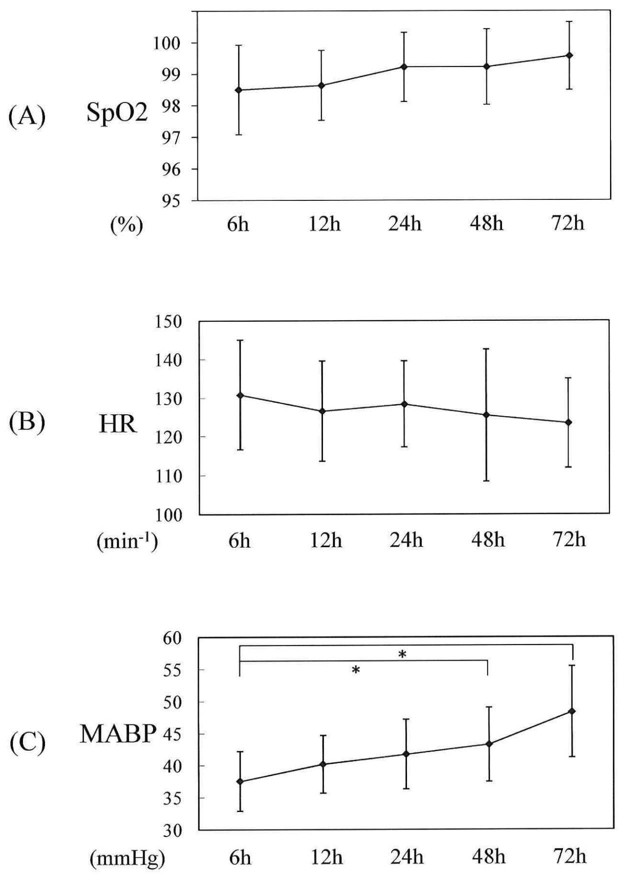

Fig. 1 Longitudinal changes in oxygen saturation (SpO_2) (A), heart rate (HR) (B) and mean arterial blood pressure (MABP) (C).
There were no significant changes in SpO2 or HR during the study period.
MABP gradually increased after birth, and significantly increased from 6 hrs to 48 and 72 hrs. **p*<0.05

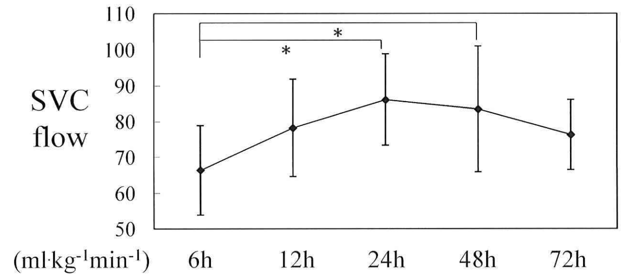

Fig. 2 Longitudinal changes in superior vena cava flow (SVC flow).
SVC flow showed a relatively low value at 6 hrs and then gradually increased until 24 hrs, showing a peak value at 24 hrs. SVC flow at 6 hrs after birth significantly decreased at 24 and 48 h. **p*<0.05

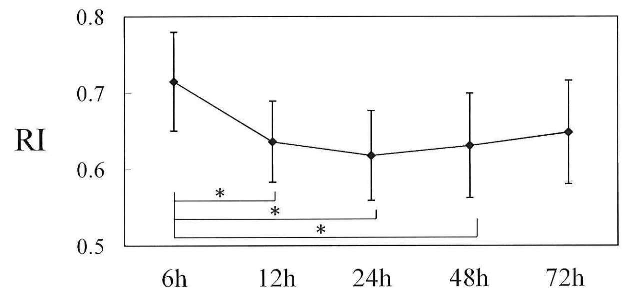

Fig. 3 Longitudinal changes in the resistance index of the anterior cerebral artery (RI-ACA). RI-ACA showed a relatively high value at 6 hrs after birth and then gradually decreased until 24 hrs, showing a low value at 24 hrs. RI-ACA at 6 hrs after birth significantly increased at 12, 24 and 48 hrs. **p*<0.05

The time course of changes in SpO_2, HR and MABP were shown in Fig. 1. There were no significant changes in SpO_2 and HR during the study period. MABP gradually increased after birth, and significantly increased from 6 hrs to 48 and 72 hrs. (37.5[4.7] vs 43.3[5.8], 48.4[7.1] : p<0.05).

The time course of changes in SVC flow were shown in Fig. 2. The SVC flow showed a relatively low value at 6 hrs and then gradually increased until 24 hrs, showing a peak value at 24 hrs. SVC flow at 6 hrs after birth significantly decreased at 24 and 48 hrs. (67.9[20.0] vs 83.9[13.5], 80.5[16.9] : p<0.05).

The time course of changes in RI-ACA are shown in Figure 3. RI-ACA showed a relatively high value at 6 hrs after birth and then gradually decreased until 24 hrs, showing the lowest value at 24 hrs. RI-ACA at 6 hrs after birth significantly increased at 12, 24 and 48 hrs (0.71[0.06] vs 0.64[0.05], 0.62[0.06], 0.63[0.07] : p <0.05).

The time course of changes in TOI and FTOE were shown in Fig. 4. TOI showed a relatively low value at 6 hrs after birth, then gradually increased until 24 hrs, therefore gradually decreasing until 72 hrs. TOI at 6 hrs after birth significantly decreased at 24 and 48 hrs (58.0[3.6] vs 62.1[3.0], 61.7[4.0] : p<0.05). FTOE showed a relatively high value at 6 hrs after birth, gradually decreased until 24 hrs, then gradually increased until 72 hrs. FTOE at 6 hrs after birth significantly increased at 24 and 48 hrs (0.41[0.03] vs 0.36[0.03], 037[0.04] : p <0.05).

The regression analysis between TOI and SVC flow is shown in Fig. 5. There was a positive correlation between them (r=0.61, p<0.05), and no significant correla-

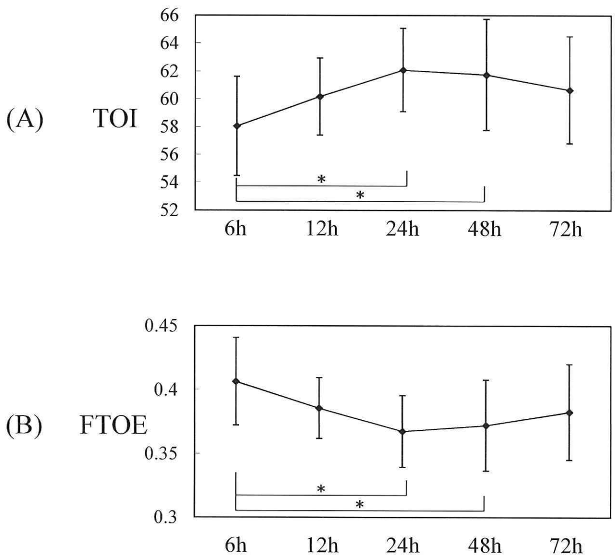

Fig. 4 Longitudinal changes in cerebral tissue oxygenation index (TOI) (A) and cerebral fractional tissue oxygen extraction (FTOE) (B). TOI showed a relatively low value at 6 hrs after birth and then gradually increased until 24 hrs. TOI at 6 hrs after birth significantly decreased at 24 and 48 hrs. *$p<0.05$
FTOE showed a relatively high value at 6 hrs after birth and then gradually decreased until 24 hrs. FTOE at 6 hrs after birth significantly increased at 24 and 48 hrs. *$p<0.05$

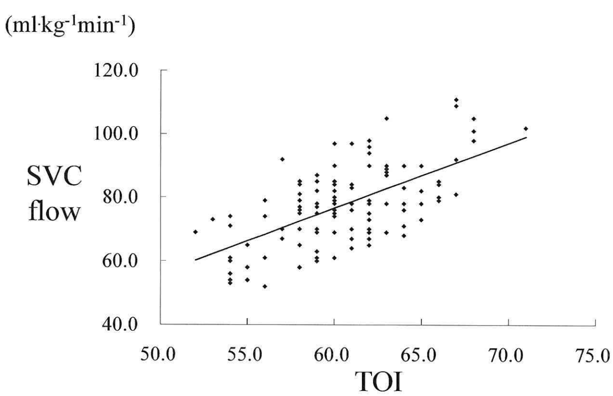

Fig. 5 The relationship among the TOI and SVC flow, MABP and all other measurements
There was a positive correlation between the TOI and SVC flow ($r=0.61$, $p<0.05$)
There were no significant correlation between MABP and all other measurements.

tion between MABP and all other parameters.

Discussion

Among healthy term newborn infants, we compared the time cause of changes between the cerebral perfusion measured by TOI, FTOE, RI-ACA and the systemic perfusion measured by SVC flow and MABP within 72 hrs after birth. The RI-ACA which evaluates vascular resistance in the brain and the FTOE which represents the ratio of oxygen consumption in cerebral tissues showed a high value at 6 hrs after birth, and then decreased till 24 hrs after birth. The TOI which indicates cerebral oxygenation, and SVC flow which indicates the blood flow of the upper body showed low value at 6 hrs after birth, and then increased, showing a peak value at 24 hrs after birth. A positive correlation was observed between TOI and SVC flow. There was no correlation between MABP and the other four measurements.

NIRS is a useful procedure to continuously measure O_2Hb, HHb and cHb non-invasively. The TOI is a parameter for the evaluation of oxygenation and the metabolic state[10]. Changes in the TOI are determined mainly by changes in Hb, SpO_2, and blood flow in a clinical setting. Among infants with stable Ht and SpO_2 values, changes in the TOI may reflect the change in blood flow[11)12)]. Naulaers et al. showed that there was a significant increase in the median TOI over the first 3 days of life in 15 very low birth weight infants : 57% on day 1, 66.1% on day 2, and 76.1% on day 3[13]. They explained that this increase in the TOI might reflect an increase in CBF during this period because the subjects were managed under stable conditions. Since the subjects of the study are stable newborn infants without IVH, the decrease in cerebral TOI during the early postnatal period might reflect a decrease in cerebral blood flow (CBF). Therefore, the cerebral blood volume showed a low value in healthy term newborn infants immediately after birth, and then gradually increased. RI-ACA is thought to be a parameter which evaluates cerebral perfusion resistance in newborn infants[9]. This parameter shows high values in patients with increased vascular resistance by cerebral edema. This also shows low values in patients with decreased vascular resistance by HIE. In our study, the increase of RI-ACA in 27 subjects during the early postnatal period might be caused by the condition of cerebral edema by mechanical stress at birth.

The cerebral fractional oxygen extraction (FOE), which represents the ratio of oxygen uptake to oxygen delivery is another parameter of cerebral oxygenation. Naulaers et al.[4] recently showed a close correlation between the FTOE measured by NIRS and the actual FOE in piglets, and concluded that FTOE is likely to provide important continuous information on oxygenation status of the brain. In our study, the TOI decreased and the FTOE increased immediately after birth. Increased cerebral FTOE reflects increased oxygen extraction by the brain tissue and suggests that the oxygen consumption exceeds the rate of oxygen delivery. Increased FTOE may indicate a compensatory mechanism for the decreased cerebral tissue oxygenation associated with reduced CBF and reduced oxygen delivery[14].

The cardiac output evaluated by Doppler echocardiographic measurement is useful to evaluate systemic blood volume non-invasively. However, the effect of ductal shunts on left ventricular output and of atrial shunts (foramen ovale) on right ventricular output cause either of these measures to overestimate the real systemic blood flow[15]. Kluckow and Evans recently proposed that SVC flow is a consistent marker of upper body perfusion, which is not affected by the shunting that occurs at both ductal and atrial level in newborn infants immediately after birth. They also reported that the SVC flow is a useful parameter to evaluate cerebral perfusion because approximately 80% of this flow returns from the brain[8]. Their detailed clinical study reported that preterm ill infants who showed a period of low SVC flow during the first 24 postnatal hours developed severe IVH[16]. We measured the time course of changes in SVC flow in healthy term newborn infants in this study, and compared this parameter with TOI which is a marker of cerebral oxygenation and blood flow. Both parameters showed a low value during the early postnatal period and then gradually increased, and a significant correlation was observed between them. This is probably because the TOI reflects venous oxygen saturation, especially of the jugular vein which is located upstream of the SVC[17]. Since the low value of SVC flow means a decrease in upper body perfusion, the decrease of cerebral blood volume in healthy term newborn infants immediate after birth is likely to be caused not only by cerebral edema but also by decrease of systemic blood volume.

The changing pattern of MABP in our study was not similar to that of either TOI or SVC flow which are parameters of cerebral and systemic perfusion. There is a possibility that the MABP did not evaluate the systemic perfusion correctly by the effect of ductal shunt, especially during the immediate postnatal period. Fluctuations of cardiac output caused by the ductal shunt flow is due to the pulmonary vascular resistance, but not due to the peripheral vascular resistance, that is, blood pressure[18)19]. Some recent reports showed that new born infants with hypoxia-ischemia after severe birth asphyxia had transient increase in CBF during acute phase[20)21]. In this respect, serial and detailed monitoring in cerebral perfusion immediately after birth might be useful for management such as providing predictive values of early parameters. The measurements of TOI and FTOE using NIRS, and SVC flow using echocardiography might be useful parameters for noninvasive bedside assessment of cerebral perfusion in neonates.

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正期産新生児における生後早期の脳循環の評価

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正期産新生児27例を対象に生後6、12、24、48、72時間において、近赤外線分光法（NIRS ; Near-infrared spectroscopy）と超音波診断装置（エコー）を用いて脳循環と体循環の経時的評価を行った。脳組織酸素化指標 Tissue oxygenation index（TOI）と上半身の血液環流を評価する上大静脈血流量（SVC flow）は生後6時間で低値を認めた後、徐々に上昇し生後24時間で最高値を示した。前大脳動脈血流の抵抗を評価する Resistance index（RI）と脳組織での酸素抽出率の指標となる fractional tissue oxygen extraction {FTOE=(Sp_2O − TOI)/Sp_2O} は生後6時間で高値を示した後、生後24時間まで低下する変化を示した。また、TOI と SVC flow の間で有意な相関が認められた。平均血圧（MABP）は生後6時間より徐々に上昇する有意な変化がみられたが、その他の測定因子との間に相関関係は認められなかった。出生直後の正期産新生児では脳組織酸素の低下および血液量の低下が認められ、これらの変化は出産ストレスに伴う脳浮腫の影響や、胎外循環への適応過程における循環血液量の変化による影響の可能性が示唆された。NIRS による TOI および FTOE 測定と心エコーによる SVC flow 測定は、新生児の非侵襲的な脳循環評価法として有用であると考えられた。

〈キーワード〉 新生児、近赤外線分光法（NIRS）、組織酸素化指標（TOI）、心臓超音波検査（心エコー）、脳血流量（CBF）