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Pediatrics 2006;117:333-339

DOI: 10.1542/peds.2005-0987

This information is current as of March 29, 2006

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<http://www.pediatrics.org/cgi/content/full/117/2/333>

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Cerebral Oxygenation and Electrical Activity After Birth Asphyxia: Their Relation to Outcome

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

OBJECTIVE. To determine the value of regional cerebral oxygen saturation (rSO_2), fractional cerebral tissue oxygen extraction (FTOE) measured by near-infrared spectroscopy (NIRS), and amplitude integrated electroencephalogram (aEEG) after birth asphyxia in relation to neurodevelopmental outcome.

METHODS. NIRS measured rSO_2 , FTOE, and aEEG were monitored simultaneously, together with arterial oxygen saturation (SaO_2) and blood pressure during the first 48 hours after severe birth asphyxia in 18 term infants. FTOE was calculated as $[SaO_2 - rSO_2]/SaO_2$. Neurodevelopmental outcome was assessed at 3, 9, and 18 months and 3 and 5 years of age. At the time points 6, 12, 18, 24, 30, 36, 42, and 48 hours after birth, the mean values of SaO_2 , rSO_2 , FTOE, and mean arterial blood pressure were calculated over a 1-hour period. A stepwise-regression model was used to investigate the relative contribution of rSO_2 , FTOE, or aEEG to developmental outcome.

RESULTS. Nine infants died during the neonatal period as a result of neurologic deterioration, and 8 infants had a normal outcome at 5 years of age. One child developed learning disabilities and a mild diplegia. The rSO_2 and FTOE remained stable in infants with a normal outcome. The rSO_2 increased and the FTOE decreased after 24 hours in the infants with an adverse outcome. (rSO_2 : 65% vs 84% at 12 and 48 hours, respectively; FTOE: 0.32 vs 0.12 at 12 and 48 hours, respectively). aEEG showed the closest relationship with outcome, but also rSO_2 showed a significant correlation 24 hours after birth.

CONCLUSIONS. rSO_2 and FTOE seem to reflect secondary energy failure. aEEG showed the closest relationship with outcome after severe birth asphyxia.

www.pediatrics.org/cgi/doi/10.1542/peds.2005-0987

doi:10.1542/peds.2005-0987

Key Words

birth asphyxia, cerebral oxygen saturation, fractional cerebral oxygen extraction, aEEG, neurodevelopmental outcome

Abbreviations

HIE—hypoxic-ischemic encephalopathy

aEEG—amplitude integrated electroencephalogram

NIRS—near-infrared spectroscopy

rSO_2 —regional cerebral oxygen saturation

SaO_2 —arterial oxygen saturation

FTOE—fractional cerebral tissue oxygen extraction

FT—flat tracing

CLV—continuous extremely low voltage

BS—burst suppression

DNV—discontinuous normal voltage

CNV—continuous normal voltage

MABP—mean arterial blood pressure

Accepted for publication Jun 27, 2005

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2006 by the American Academy of Pediatrics

THE INCIDENCE OF hypoxic-ischemic encephalopathy (HIE) has remained constant over the past 4 decades and varied between 1 and 6 per 1000 live births (3–4 per 1000 live births¹; 1–6 per 1000 live births²) Therapeutic intervention to reduce delayed neuronal death or programmed cell death after birth asphyxia may become possible within the next few years.^{3–8} In this respect, the predictive value of early parameters such as fetal heart monitoring, umbilical artery acidemia, Apgar scores, or the combination of these 3 variables has been reported to have only limited value.^{9,10} Important predictors of an adverse outcome, available in the first hours, were delayed onset of breathing, administration of chest compression at birth, and seizures. On the basis of predicted probabilities of >.50, the sensitivity of the predictive model was 85% with a specificity of 68% at 60 minutes of age.¹¹

Imaging techniques, such as cranial ultrasound and MRI, are useful for prognosis but not until 24 hours or more after birth.^{12–14} Neurophysiology, evoked potentials,¹⁵ and, more commonly used, the EEG, are widely known to be of value within the first 24 hours.^{16–18}

Single-channel amplitude integrated EEG (aEEG) is increasingly being used in NICUs, and it has been shown that aEEG has a high concordance with multichannel standard EEG,¹⁹ with a high prognostic value after birth asphyxia as early as 3 hours after birth.^{20–25} Therefore, this technique is used to improve specificity of case selection and to control severity of the injury of patients for neuroprotective intervention after birth asphyxia.⁸

Also, near-infrared spectroscopy (NIRS), monitoring noninvasively cerebral hemodynamics and oxygenation, has a potential to be used as a prognostic tool.^{26–28} In the experimental research setting it has been shown that NIRS-measured changes in oxygenated, deoxygenated, and total hemoglobin are used to estimate cerebral blood volume and cerebral blood flow and can give an indication of cerebral oxygenation.²⁹ It further showed that specially patterns of changes in oxygenation of hemoglobin were related to the severity of brain damage.^{5–7} However, practical limitations, in particular fixation problems of the sensors leading to movement artifacts, prohibit us to use the above-mentioned relative parameters during more extended periods in the clinical situation.

NIRS-measured regional cerebral oxygen saturation (rSo₂) is a reliable estimator for changes in tissue cerebral oxygenation.^{30–32} Because absolute values are provided here, rSo₂ is much less dependent on movement artifacts, and comparisons over extended periods of time are possible in the clinical situation. Fractional cerebral tissue extraction (FTOE) then can be calculated from rSo₂ and arterial oxygen saturation (SaO₂)^{31,32} (see also “Methods”).

Because both rSo₂ and FTOE are stable parameters and are monitored easily and noninvasively in the clin-

ical setting,^{32,33} we initiated a clinical study to determine the value of rSo₂ and FTOE measured by NIRS in the first 48 hours after birth asphyxia in relation to neurodevelopmental outcome and compare their prognostic value with aEEG.

METHODS

Term infants who had severe birth asphyxia and a gestational age >37 weeks and were admitted to our tertiary NICU within 24 hours after birth were selected for this study. The children received a diagnosis of asphyxia when they met at least 3 of the following criteria: (1) signs of intrauterine asphyxia, as indicated by late decelerations on fetal monitoring or by meconium staining of the amniotic fluid; (2) arterial cord blood pH <7.10; (3) delayed onset of spontaneous respiration and need for artificial ventilation for at least 5 minutes; (4) Apgar score of ≤5 at 5 minutes; or (5) multiorgan failure. Neonates with infections of the central nervous system, congenital abnormalities, chromosomal disorders, or longstanding hypoglycemia were excluded.

After admission, an aEEG (Cerebral Function Monitor, CFM 4640; Lectromed, Devices Ltd, Oxford, United Kingdom) together with the NIRS (INVOS 4100; Somanetics Corp, Troy, MI) was applied by the attending neonatologist. Informed parental consent was obtained in all cases. The aEEG and NIRS recording was continued for a minimum duration of 48 hours. Heart rate, arterial blood pressure, and SaO₂ were measured simultaneously with NIRS and aEEG. All variables were collected simultaneously and stored on a personal computer for offline analysis (software: Poly 5; Inspektor Research Systems, Amsterdam, the Netherlands), with a sampling frequency of 10 Hz. The study was approved by the ethical committee of our hospital. HIE was classified according to the criteria of Sarnat and Sarnat.³⁴

Monitoring of Cerebral Oxygenation Using NIRS

For noninvasive monitoring of cerebral hemodynamics and oxygenation, transcranial NIRS was used (INVOS 4100). A self-adhesive transducer that contained the light-emitting diode and 2 distant sensors were fixed on the left parietal side of the neonatal skull.^{35,36} For assessment of cerebral oxygenation, rSo₂ was calculated from the differential signal obtained from these 2 sensors, expressed as the venous-weighted percentage of oxygenated hemoglobin (oxygenated hemoglobin/total hemoglobin [oxygenated hemoglobin + deoxygenated hemoglobin]).^{33,37}

Because absolute values are provided here, rSo₂ is less dependent on movement artifacts, and comparisons over time are possible.^{31,37} FTOE can be calculated from rSo₂ and SaO₂. For investigation of the balance between oxygen delivery and oxygen consumption, a relative FTOE measurement can be formulated as a ratio: (SaO₂ – rSo₂)/SaO₂. An increase in FTOE reflects an increase of the oxygen extraction by brain tissue, suggesting a

higher oxygen consumption in relation to oxygen delivery. Conversely, a decrease of FTOE suggests less utilization of oxygen by brain tissue in comparison with the supply.³¹

Monitoring of aEEG

An aEEG, the cerebral function monitor (CFM 4640), was applied to monitor electrical brain activity. The CFM records a single-channel EEG from 2 parietal electrodes. The filtered signal is rectified, smoothed, and amplitude integrated. Specifically, different aEEG patterns by means of pattern recognition are looked at: flat tracing (FT; very low voltage, mainly inactive [isoelectric] tracing with activity below 5 μ V); continuous extremely low voltage (CLV; continuous background pattern of very low voltage [approximately or below 5 μ V]); burst suppression (BS; discontinuous background pattern; periods of very low voltage [inactivity] intermixed with burst of higher amplitude); discontinuous normal voltage (DNV; discontinuous trace, whereby the voltage is predominantly >5 mV); continuous normal voltage (CNV; continuous activity with voltage 10–25 [–50] μ V).^{19,20}

Epileptic activity could also be identified. Epileptiform activity (characteristic pattern, with increased amplitude during epileptic seizure activity and lower voltage in the postictal period) was classified as follows: single seizure, repetitive seizures (≥ 3 discharges during a 30-minute period), and status epilepticus (“sawtooth pattern”). The traces were analyzed off-line. Both the background activity and the presence of seizure activity were taken into account when the data were analyzed.

Assessment of Neurodevelopmental Outcome

The survivors were seen in the follow-up clinic at 3, 9, and 18 months and 3 and 5 years. The physicians who perform the follow-up are blinded to the results of aEEG and FTOE/rSO₂. Assessment of outcome was performed using the Griffiths Mental Developmental Scale³⁸ and items from Amiel-Tison and Grenier³⁹ and Touwen⁴⁰. The AIMS was used during the first 18 months of age, and the Movement ABC was used at 5 years of age to assess motor function further.⁴¹

A full neurologic assessment was performed at each visit to the follow-up clinic, and cerebral palsy was classified according to the criteria of Hagberg et al.¹ Global delay was considered when there was a developmental quotient <85, obtained at 18 to 24 months of age, using the Griffiths Mental Developmental Scale.

Study Design

At the time points 6, 12, 18, 24, 30, 36, 42, and 48 hours after birth, the mean values of SaO₂, rSO₂, FTOE, and mean arterial blood pressure (MABP) were calculated over a 1-hour period. At the same time points, the background pattern of the aEEG was analyzed off-line. To analyze the aEEG data, we used a scoring system representing the different background patterns: CNV,

score 5; DNV, score 4; BS, score 3; CLV, score 2; and FT, score 1.

Statistical Analysis

Data are summarized as means \pm SD or as median and ranges as appropriate. Differences in clinical data and blood pressure between infants with favorable or adverse outcome were compared by Student's *t* test or χ^2 test, as appropriate. Differences over postnatal age of rSO₂, FTOE, and the aEEG score within groups were assessed with analysis of variance for repeated measurements, followed by the Scheffe's procedure when a significant difference was found. The Mann-Whitney *U* test was used to assess changes of rSO₂, FTOE, and the aEEG score between groups at various points of time. Stepwise-regression analysis (forward procedure) was used to reveal whether outcome, defined as favorable or adverse (dependent variable), was related to rSO₂, FTOE, or the aEEG score (independent variables). This statistical model was chosen because it selects the independent variable that is most predictive of the dependent variable (highest correlation with dependent variable [in our case outcome] and indicated by the height of the F value). To illustrate the relations between aEEG on the one hand and rSO₂ and FTOE on the other hand, simple linear regression was performed. For statistical analysis, Statview II was used (Abacus Concepts, Inc, Berkeley, CA). Statistical significance was assumed for *P* < .05.

RESULTS

Twenty-two patients were originally enrolled in the study. One infant had to be excluded during follow-up because a syndrome was being diagnosed. In 3 infants, the NIRS data were not available before 24 hours after birth. Eventually, the data of 18 infants were used for the present study. Fifteen infants were outborn patients. Nine infants died in the neonatal period, after severe neurologic deterioration. They were classified as adverse outcome. Eight of them had an HIE grade III according to Sarnat and Sarnat,³⁴ and 1 infant had a grade II encephalopathy. Two patients (patients 3 and 17) died within 48 hours after birth. Median age at initiation of the study was 5 hours. It is our policy to withdraw intensive care when a combination of neurophysiology (aEEG, standard EEG, evoked potentials [somatosensory evoked potential and visual evoked potential]), and cerebral imaging (ultrasound, MRI) remains severely abnormal on 2 or more occasions and all point to severe brain damage.

The remaining 9 infants had a follow-up of at least 2 years. Seven of them had an HIE grade II. In 2 patients, the severity of the HIE could not be determined because of muscle paralysis. Median age at initiation of the study was 2 hours. Eight children had a normal developmental quotient (range: 93–128). These children were classified as having a favorable outcome. One child (patient 11) with learning disabilities also had a very mild diplegia.

He had venous infarction of antenatal origin and a ventricular dilation in the neonatal period. Patient characteristics and follow-up data of the 18 infants are listed in Table 1.

MABP and SaO_2 were measured simultaneously with NIRS and aEEG and could be maintained within normal limits in all patients, with or without inotropic support (Table 1). Eleven infants needed inotropic support to maintain a MABP >40 mm Hg. Maximum serum creatinine levels in each patient varied between 80 and 320 $\mu\text{mol/L}$ in the adverse-outcome group versus 31 to 213 $\mu\text{mol/L}$ in the favorable-outcome group. Maximum serum aspartate aminotransferase and alanine aminotransferase levels varied between 80 and 478 U/L and 23 to 140 U/L in the adverse-outcome group versus 108 to 396 U/L and 58 to 93 U/L in the favorable-outcome group.

Lesions were detected using neuroimaging techniques (ultrasound days 1, 2, 3, 5, and 7 and MRI days 4–7). Only 6 of these infants had an MRI during the first week of life as well, because they either were too ill to be transported or died before the MRI was done. The results are listed in Table 1. Seven infants showed abnormalities in the basal ganglia and thalami region. In 1 infant (patient 2), the cranial ultrasound scan was too early (within 24 hours) for the abnormalities to evolve. Four

infants had abnormalities in the subcortical white matter region, and 3 infants had abnormalities in the periventricular white matter region. One infant had an intraventricular hemorrhage with a venous infarction and dilation of the ventricle that needed drainage. The images of 2 infants did not show any abnormalities.

NIRS

The rSo_2 values remained normal and stable in infants with a normal outcome with values between 50% and 70%^{30,33} but increased to supranormal values after 24 hours in the infants with an adverse outcome (Fig 1). From 24 hours onward, the values of rSo_2 of the infants with an adverse outcome were significantly higher as compared with those with a favorable outcome (24 hours: $P < .05$; 30 hours: $P < .001$; 36 hours: $P < .001$; 48 hours: $P < .001$). Values of rSo_2 in the adverse-outcome group increased significantly in time ($P < .001$, 48 vs 12 hours).

The FTOE ($[SaO_2 - rSo_2]/SaO_2$) remained stable as well in infants with a normal outcome but decreased after 24 hours in the infants with an adverse outcome (Fig 2). From 24 hours onward, the values of FTOE of the infants with an adverse outcome were significantly lower as compared with those with a favorable outcome (24 hours: $P < .05$; 30 hours: $P < .001$; 36 hours: $P < .001$).

TABLE 1 Patient Data

Patient	GA, wk	Birth Weight, g	5-min Apgar Score	Start of Monitoring, h	Cranial Ultrasound	Time CNV/SW, h	MRI	Follow-up DQ	Clinical Diagnosis	Respiratory Support	Circulatory Support
1	40	3175	7	7	SCL	–		^b	HIE 3/seizures	Prim, PPHN	Dopa
2	38	3250	2	3.5	Normal ^a	–		^b	HIE 3/seizures	Prim, PPHN	Dopa, dobuta, adren
3	39	3600	5	1	BGT	–	BGT	^b	HIE 3/seizures	Prim	Dopa
4	40	4150	2	2	BGT	–	BGT	^b	HIE 3/seizures	Prim	–
5	39	3415	5	21	SCL	–		^b	HIE 3/seizures	Sec	–
6	40	4090	2	19	SCL	–		^b	HIE 3/seizures	Sec	–
7	40	3580	6	10	Normal	12		128	Asphyxia/paralyzed	Prim, PPHN, HFO, NO	Dopa, isoprel
8	37	2240	6	4	WML	30		93	HIE 2	Prim, PPHN, HFO	Dopa, dobuta, corticosteroids
9	39	2550	3	8	WML transient	12/30	Subtle WML	99	HIE 2/seizures	Prim	–
10	41	3250	1	2	WML	3		103	HIE 2/seizures	Prim	Extra fluid
11	40	3080	6	2	IVH+VI/PHVD	3	WML	99 mild diplegia	HIE 2/seizures/IVH venous infarction/PHVD	Prim	Dopa, dobuta, isoprel
12		2555	2	1	SCL transient	6/6		112	HIE 2/seizures	–	Dopa
13	40	3450	5	2	Normal	3		116	Asphyxia/paralyzed	sec, PPHN	Dopa, dobuta
14	39	2950	5	1	BGT	12/48	BGT	114	HIE 2/seizures	Prim	Dopa
15	41	2950	2	5	BGT	18	BGT	95	HIE 2/seizures	Prim	Dopa
16	39	4850	6	3	BGT	–		^b	HIE 3/seizures	Prim	–
17	39	3320	4	5	BGT	–		^b	HIE 3/seizures	Prim	–
18	40	3175	7	16	BGT	–		^b	HIE 2/seizures	Prim	Dopa

GA indicates gestational age; SCL, subcortical lesions; BGT, basal ganglia and thalami; WML, white matter lesions; IVH, intraventricular hemorrhage; PHVD, posthemorrhagic ventricular dilation; VI, venous infarction; CNV, continuous normal voltage; SW, sleep/wake cycling; DQ, developmental quotient; Prim, primarily, immediately after birth; Sec, secondary; PPHN, pulmonary hypertension of the neonate; HFO, high-frequency oscillation; NO, nitric oxide; dopa, dopamine; dobuta, dobutamine; isoprel, isoprenaline.

^a This infant died within 24 hours after birth, before the abnormalities on ultrasound could evolve.

^b These patients died in the neonatal period.

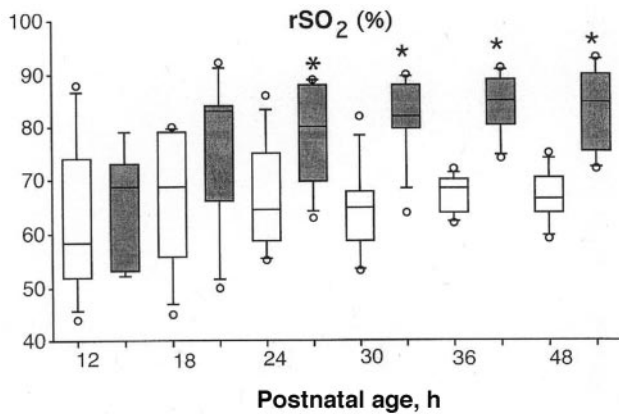


FIGURE 1
rSO₂ at different time points after birth asphyxia: adverse (■) versus good (□) outcome.

.001; 48 hours: $P < .001$). The value of FTOE in the adverse-outcome group decreased significantly in time ($P < .001$, 48 vs 12 hours).

aEEG

From 12 hours after birth, we had enough data to compare the 2 groups, the ones with a good outcome versus the ones with an adverse outcome (Fig 3). The aEEG was significantly different in both groups at every time point (12 hours: $P < .001$; 18 hours: $P < .001$; 24 hours: $P < .001$; 30 hours: $P < .001$; 36 hours: $P < .001$; 48 hours: $P < .001$).

The time of onset of CNV is listed in Table 1. Sleep/wake cycling could be identified only in 3 infants during the 48-hour study period. All of these infants were normal at follow-up.

Epileptiform activity could be identified on the aEEG recordings in 15 infants. Six of them were normal at follow-up. The data concerning epileptic activity were part of another study and did not influence the results of the present study.

No correlation was detected between aEEG on the

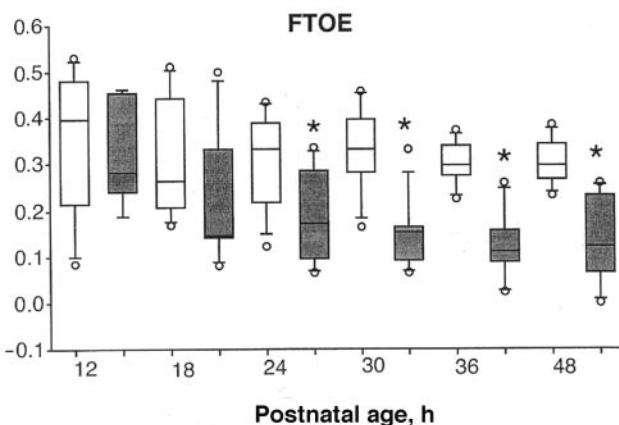


FIGURE 2
FTOE at different time points after birth asphyxia: adverse (■) versus good (□) outcome.

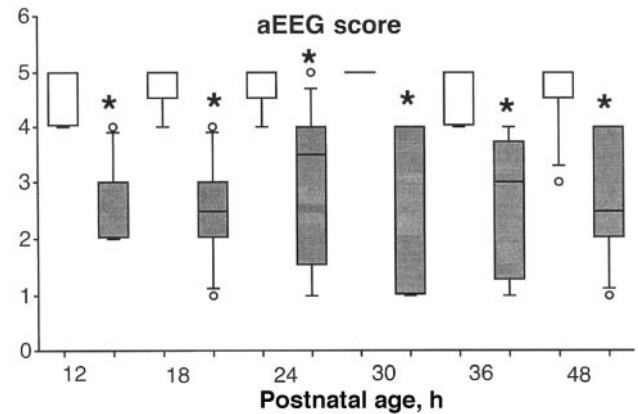


FIGURE 3
Score of aEEG at different time points after birth asphyxia: adverse (■) versus good (□) outcome. CNV = score 5; DNV = score 4; BS = score 3; CLV = score 2, and FT = score 1.

one hand and rSO₂ or FTOE on the other hand during the first 24 hours of life. However, a weak correlation developed for aEEG and rSO₂ ($r = -0.38$; $P < .001$) and for aEEG and FTOE ($r = 0.37$; $P < .001$) when the whole study period (48 hours) was included.

Stepwise-Regression Analysis

Stepwise-regression analysis showed that the aEEG score seemed to be the most significant independent variable to affect the regression model and the most strongly related to the dependent variable outcome (F test: 123.28). Also, rSO₂, as a measure of cerebral oxygenation, entered the regression equation and was related to the dependent variable outcome, albeit with a lower F value (F test: 90.18). FTOE as a measure of cerebral oxygen extraction, however, was removed from the regression model. This indicates that the aEEG score was most closely related to neurodevelopmental outcome.

DISCUSSION

This study showed that rSO₂ and FTOE remained stable in infants with a normal outcome but increased and decreased respectively after 24 hours in infants with an adverse outcome, after birth asphyxia. aEEG showed the closest relationship with outcome, which is consistent with earlier studies.²¹⁻²³

The interpretation of the increase over postnatal time of rSO₂, an indicator for mixed arteriovenous oxygenation of the brain, and the decrease of FTOE, an estimator of oxygen extraction of the brain tissue, in the infants with adverse neurodevelopmental outcome can be 2-fold. First, it may indicate a birth asphyxia-induced vasoparalysis of the resistance vessels of the arterial cerebral vascular bed with profound vasodilation. This is reported extensively after hypoxia-ischemia.⁴² This phenomenon causes a mismatch between the cerebral blood flow-regulated oxygen consumption of brain tissue. Meek et al²⁷ showed indeed an increase of NIRS-meas-

sured cerebral blood volume, within certain limits an estimator of changes in actual cerebral blood flow,⁴³ on the first day of life after severe asphyxia in infants with adverse outcome. This phenomenon of early asphyxia-related vasodilation is supported further by Doppler-related studies performed in severely asphyxiated infants.^{44,45} An older study of our group⁴⁵ found a lower vascular resistance as indicated by the resistance index. From birth up to 96 hours of age (with the lowest value between 24 and 60 hours) the course of the resistance index showed indeed some resemblance with the course of rSO₂ and FTOE as indications of cerebral oxygenation and extraction. The rSO₂ remains elevated and stable after 24 hours, in contrast to resistance index.

The second and more reliable explanation is that the combination of increase of rSO₂ and decrease of FTOE reflects less utilization of oxygen of brain tissue as a result of neuronal cell death with a consequent decrease in uptake of oxygen by the brain. From clinical experience in adults with stroke, it is known that oxygenation (rSO₂) measured in the infarcted region showed supranormal levels, which was explained by the fact that injured or dead neurons consume little or no oxygen.⁴⁶ Experimental studies in newborn piglets with hypoxia-ischemia showed reoxygenation and reperfusion and initial hyperperfusion of the brain and recovery of oxidative metabolism. However, in animals that developed extensive brain damage, oxidative metabolism decreased to abnormally low values from 24 hours up to 48 to 72 hours after the actual insult. This was explained by secondary energy failure, leading to delayed neuronal cell death with consequently less utilization of oxygen.^{6,47} This pattern of secondary energy failure was confirmed in the human infant with severe birth asphyxia and adverse outcome by Cady et al.⁴⁸ The pattern of increased cerebral oxygenation as indicated by rSO₂ and decrease in oxygen utilization as indicated by a decrease in FTOE, starting at 24 hours and evolving over the next 24 hours as shown in the present study, fits nicely with the occurrence of secondary energy failure in the infants with neurologic deterioration and adverse outcome. We therefore suggest that the patterns of rSO₂ and FTOE indeed indicate secondary energy failure with less utilization of oxygen, rather than indicating vasoparalysis.

In contrast to the relatively late (from 24 hours onward) derailment of the patterns of rSO₂ and FTOE of the asphyxiated infants with adverse outcome, this study confirms an earlier study of our group in which the pattern of aEEG predicted outcome already at an early postnatal age and is the parameter most closely related to outcome.²³ This underscores once again the importance of aEEG as a reliable prognostic tool. Moreover, it may prove to be of value to assess the effect of intervention studies such as selective head cooling⁸ and pharmacologic interventions.³ Finally, early detection and treat-

ment of epileptic activity may be crucial in reduction of additional injury of the brain.^{49,50}

The mortality in the present study was high (50%). This reflects the severity of the HIE of this particular group with severe birth asphyxia. Except for 2 patients in which the severity of HIE could not be determined because of muscle paralysis, they all had an HIE grades II and III with seizures in 15 of the 18 infants.

CONCLUSIONS

We suggest that rSO₂, as a measure of cerebral oxygenation, and FTOE, as a measure of oxygen extraction by brain tissue, can be monitored in a noninvasive, easy, and reliable manner over extended periods of time and reflect metabolic disturbances such as secondary energy failure after severe birth asphyxia. Moreover, together with aEEG, which showed the closest relationship with outcome, these parameters (especially FTOE) have a prognostic value after severe birth asphyxia.

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Pediatrics 2006;117:333-339
DOI: 10.1542/peds.2005-0987

This information is current as of March 29, 2006

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