The Relationship Between Electrocerebral Activity and Cerebral Fractional Tissue Oxygen Extraction in Preterm Infants

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ABSTRACT: Impaired cerebral oxygen delivery may cause cerebral damage in preterm infants. At lower levels of cerebral perfusion and oxygen concentration, electrocerebral activity is disturbed. The balance between cerebral oxygen delivery and oxygen use can be measured by near-infrared spectroscopy (NIRS), and electrocerebral activity can be measured by amplitude-integrated EEG (aEEG). Our aim was to determine the relationship between regional cerebral tissue oxygen saturation (r_cSO_2), fractional tissue oxygen extraction (FTOE), and aEEG. We recorded longitudinal digital aEEG and r_cSO_2 prospectively in 46 preterm infants (mean GA 29.5 wk, SD 1.7) for 2 hr on the 1st to 5th, 8th, and 15th d after birth. We excluded infants with germinal matrix hemorrhage exceeding grade I and recordings of infants receiving inotropes. FTOE was calculated using transcutaneous arterial oxygen saturation ($tcSaO_2$) and r_cSO_2 values: $(tcSaO_2 - r_cSO_2)/tcSaO_2$. aEEG was assessed by calculating the mean values of the 5th, 50th, and 95th centiles of the aEEG amplitudes. The aEEG amplitude centiles changed with increasing GA. FTOE and aEEG amplitude centiles increased significantly with postnatal age. More mature electrocerebral activity was accompanied by increased FTOE. FTOE also increased with increasing postnatal age and decreasing Hb levels. (*Pediatr Res* 70: 384–388, 2011)

Preterm infants are at risk of developing intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL) (1), two conditions that may lead to permanent cerebral damage. Impaired cerebral oxygenation may contribute to the development of both IVH and PVL and may thus contribute to the development of permanent cerebral damage (2). We defined oxygenation of the brain as oxygen delivery to the brain, which depends on cerebral perfusion and arterial oxygen content. Impaired oxygen delivery may also cause cerebral damage, independently of IVH and PVL.

The balance between cerebral oxygen delivery and oxygen use can be monitored by near-infrared spectroscopy (NIRS) (3). This is a noninvasive method that measures regional cerebral oxygen saturation (r_cSO_2). r_cSO_2 reflects the oxygen saturation in a mixed vascular bed dominated by venules. Fractional tissue oxygen extraction (FTOE) can be calculated from r_cSO_2 and transcutaneous arterial oxygen saturation ($tcSaO_2$) (4). It reflects the balance between oxygen supply and oxygen consumption and may thus indicate cerebral hypoxemia or ischemia.

At lower levels of cerebral perfusion and oxygen delivery, electrocerebral activity is disturbed. Amplitude-integrated EEG (aEEG) is a marker of electrocerebral activity. In term infants, aEEG can be severely abnormal following perinatal asphyxia (5). In preterm infants, electrocerebral activity is generally discontinuous and changes with gestational and postnatal age (6,7). With increasing gestational and postnatal age, continuous electrocerebral activity increases.

Little is known about the relationship between electrocerebral activity and cerebral oxygen delivery in relatively healthy preterm infants. Therefore, the aim of our study was to investigate the relationship between r_cSO_2, FTOE, and aEEG. We hypothesized that increased electrocerebral activity will lead to higher oxygen consumption and, as a result, to higher FTOE, as long as it is not accompanied by increased oxygen delivery.

METHODS

For this prospective observational study, we initially selected 50 preterm infants that had been admitted to the NICU of the University Medical Center Groningen between May 2006 and July 2007. All preterm infants with a GA of 26 to 32 wk admitted on their first day after birth were eligible for inclusion. We excluded infants with major chromosomal or congenital abnormalities. After the initial selection, we excluded three infants from further analysis that had developed an IVH exceeding grade I according to Volpe (8). We also excluded 11 recordings of infants that required inotropes to maintain blood pressure at the time of the aEEG and NIRS recordings. The final study cohort consisted of 46 infants. Written informed consent was obtained from both parents. The study was approved by the review board of the University Medical Center Groningen.

The aEEG and r_cSO_2 were measured simultaneously within the first 24 h after birth and subsequently on the 2nd, 3rd, 4th, 5th, 8th, and 15th d.

The aEEG measurements. We used a digital cerebral function monitor (CFM) that was not commercially available at the time of the study. It consisted of an amplifier connected to a laptop computer that contained software for digital aEEG processing. In addition to displaying the aEEG pattern, it also displayed the original EEG. The device recorded the aEEG through two neonatal ECG electrodes with a diameter of 15 mm (Neotrode II, Conmed, Utica, NY, USA). The electrodes were placed in P3 and P4 position (international 10–20 system). The common electrode was placed conveniently anywhere on the infant's body. We used a digital direct current (DC) common average reference amplifier (Porti-X by TMSi, Enschede, The Netherlands) comprising a high input impedance (>2 GΩ) and a 22-bits

Abbreviations: **aEEG,** amplitude-integrated EEG; **BS,** burst suppression; **CNV,** continuous normal voltage; **CPAP,** continuous positive airway pressure; **DNV,** discontinuous normal voltage; **FTOE,** fractional tissue oxygen extraction; **IVH,** intraventricular hemorrhage; **NIRS,** near-infrared spectroscopy; **Paco₂,** arterial partial pressure of carbon dioxide; **PDA,** persistent ductus ateriosus; **PVL,** periventricular leukomalacia; **r_cSO_2,** regional cerebral oxygen saturation; **SWC,** sleep-wake cycling; **tcSao₂,** transcutaneous arterial oxygen saturation
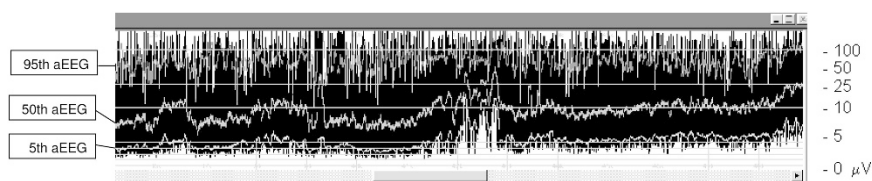
Figure 1. Example of a display of the digital recorded aEEG. 5th aEEG: 5th centile of the aEEG amplitude; 50th aEEG: 50th centile of the aEEG amplitude; 95th aEEG: 95th centile of the aEEG amplitude.

sigma-delta Analog to Digital Converter with a resolution of 0.0715 μV per bit. The electrodes were connected to the amplifier by means of shielded cables to prevent electrical noise and alternating current (AC) power interference pick-up. Loss of electrode contact was sensed by the amplifier's input circuitry and signaled to the data acquisition software. Low (<0.5 Hz) and high frequencies (>25 Hz) were attenuated by first-order high and low pass filtering. The EEG was stored on a hard disc, and the aEEGs were processed.

The aEEG processor was constructed in software and comprised a signal shaping filter, a semi-logarithmic rectifier, a peak detector, and a smoothing filter. Its characteristics were similar to the CFM constructed and described by Maynard *et al.* (9) and to all commercially available machines. All values were filtered by box-car averagers with a time window of 60 s. To obtain additional information, the mean of the aEEG amplitude and the mean peak and trough values were computed and displayed. The mean trough and mean peak values represented the 5th and 95th centiles of the aEEG amplitudes. An example of an aEEG recording, which also displays the aEEG amplitude centiles, is shown in Figure 1.

We assessed the aEEGs by pattern recognition and by calculating the centiles of the aEEG amplitudes.

While the aEEGs were being recorded, the nursing staff noted down any handling of the infant, clinical seizures, and administration of anticonvulsant or sedative drugs.

Pattern recognition. Different background patterns were distinguished according to Hellström–Westas (10). Background patterns were characterized as follows: continuous normal voltage (CNV), discontinuous normal voltage (DNV), burst suppression (BS), continuous low voltage, or flat trace.

The presence or absence of sleep-wake cycling (SWC) and the occurrence of epileptic activity were also noted down. SWC was recognized as cyclical variations in the bandwidth of the aEEG trace indicating cycling of sleep stages.

The aEEG amplitude centiles. To obtain additional quantitative measures, we calculated the mean of the 5th, 50th, and 95th centiles of the aEEG amplitude for the recording period on each day. Artifacts were identified and confirmed with the use of the raw EEG, after which they were excluded from quantitative analysis.

Near-infrared spectroscopy. r_cSO_2 was measured with the INVOS 4100 near-infrared spectrometer (Somanetics Corporation, Troy, MI) in combination with the pediatric SomaSensor. This technology is based on the fact that biological tissue is relatively transparent to near-infrared light (600–900 nm). The optical sensor measures the quantity of reflected light photons as a function of two wavelengths (730 and 805 nm) and determines the spectral absorption of the underlying tissue (11,12). NIRS differentiates oxygenated Hb from deoxygenated Hb that has distinct absorption spectra. The ratio of oxygenated Hb to total Hb reflects the regional oxygen saturation of tissue. The SomaSensor has two detectors at a distance of 3 and 4 cm from the near-infrared optode. The detector placed at 3 cm from the optode receives light scattered predominantly from scalp and skull. The detector placed at 4 cm receives light scattered from scalp, skull, and cerebral tissue. Thus, by subtraction, the two detectors measure the oxygen saturation in the underlying cerebral tissue.

r_cSO_2 was measured over a 2-h period. Fifteen minutes were allowed for the measurement to stabilize. The optical sensor was placed to the left frontoparietal side of the infant's head and held in place by elastic bandaging.

Simultaneously, we measured transcutaneous arterial oxygen saturation ($tcSaO_2$) by pulse oximetry. We calculated FTOE with the equation FTOE = ($tcSaO_2$ − r_cSO_2)/$tcSaO_2$.

Statistical analysis. SPSS software for Windows, version 14.0 (SPSS Inc. Chicago, IL), was used for all analyses. Because of normal distribution, differences in centiles of the aEEG amplitude between certain types of background patterns were analyzed using t test. Results were expressed as mean values ± SD. The Pearson correlation coefficient (two-tailed) was calculated to test the correlation between FTOE, r_cSO_2, and the centiles of the aEEG amplitude. The variables that were tested for their relationship with the aEEG amplitude centiles and FTOE were postnatal age, GA, mean arterial blood pressure, Hb level, and arterial Pco_2 ($Paco_2$). To test whether clinical data were different between subgroups of our cohort (*e.g.* infants with and without SWC), we used the Mann–Whitney U test for continuous variables

and Fisher's exact test for categorical variables. Finally, we performed a multivariate linear regression analysis to find the most significant model explaining FTOE. Variables entered the model at a significance level of $p \leq$ 0.1. A p value of <0.05 was considered statistically significant.

RESULTS

Study group. Data were collected on 46 infants whose GAs ranged from 26 to 31.9 wk (mean 29.4 ± 1.7). We obtained 238 combined recordings of aEEG and r_cSO_2. The mean daily recording time was 128 min (SD 31). Twenty-nine infants needed artificial ventilation for initial stabilization and all but one received surfactant. During 55 recordings, infants were mechanically ventilated, and nasal continuous positive airway pressure (CPAP) was given during 98 recordings. During the remaining 86 recordings, infants either received low flow *via* nasal canula or they had no respiratory support. The majority of infants could be weaned off the ventilator within 5 d. Because we do not routinely sedate infants during artificial ventilation, none of the infants received morphine during the study period. Clinical data of the study population are summarized in Table 1.

Pattern recognition. During the entire study period, the aEEG traces of the majority of infants showed the discontinuous background patterns BS or DNV (Table 2). From the 5th d after birth, the frequency of continuous patterns increased (χ^2 for trend, $p = 0.036$). SWC was present in some infants from the first day after birth and increased on the 3rd postnatal day (χ^2 for trend, $p = 0.003$). Postmenstrual age (GA + postnatal age) was significantly higher when SWC was present (30.3 *versus* 29.7 wk, $p = 0.023$). Postnatal age was also significantly higher when SWC was present (6.0 *versus* 4.6 d, $p = 0.015$).

Table 1. *Patient characteristics (n = 46)*

GA, mean (SD), wk	29.5 (1.7)
Birth weight, mean (SD), g	1311 (390)
Antenatal steroids, n (%)	44 (96)
Apgar score 5 min, mean (range)	7.4 (3–10)
Apgar score 5 min ≥7, n (%)	35 (76)
MABP, mean (SD), mm Hg	37 (6.8)
IVH	
No, n (%)	44 (96)
Grade I, n (%)	2 (4)
Initial ventilation	
Low flow, n (%)	1 (2)
Nasal CPAP/IMV, n (%)	16 (35)
Artificial ventilation, n (%)	29 (63)
Surfactant, n (%)	28 (61)
Hb, mean (SD), mmol/l	8.7 (1.6)
$Paco_2$, mean (SD), kPa	5.5 (0.9)

MABP, mean arterial blood pressure; IMV, intermittent mandatory ventilation.

Table 2. *Frequencies of aEEG background patterns and sleep wake cycling in relation to postnatal age*

aEEG, *n* (%)	Postnatal day						
	1	2	3	4	5	8	15
BS	6 (23)	7 (19)	4 (12)	3 (8)	4 (12)	1 (3)	0
DNV	17 (65)	26 (70)	25 (73)	30 (81)	26 (74)	27 (77)	23 (66)
CNV	3 (12)	4 (11)	5 (15)	4 (11)	5 (14)	7 (20)	12 (34)
SWC (%)	8 (31)	20 (54)	26 (76)	26 (70)	24 (69)	23 (66)	27 (77)

Table 3. *aEEG amplitude centiles in relation to background patterns*

aEEG (*n*)	Amplitude centiles (mean, SD)		
	5th	50th	95th
BS (40)	3.9, 0.94	9.1, 1.7	37, 7.8
DNV (174)	6.1, 1.5	12, 2.6	36.5, 10.7
CNV (25)	8.1, 1.6	14.2, 3	32, 7.2

SWC already appeared on the first day after birth. No differences were found in GA, birth weight, and Apgar scores between infants with and without SWC on the first day after birth. Infants without SWC were significantly more often treated with surfactant ($p = 0.026$) and more often artificially ventilated ($p = 0.073$).

The different background patterns had significantly different aEEG amplitude centiles (Table 3). In comparison to DNV, BS had a significantly lower mean 5th ($p < 0.001$) and 50th amplitude centile ($p < 0.001$). In comparison to CNV, the mean 5th and 50th centiles of BS were also significantly lower ($p < 0.001$), and the mean 95th centile was higher ($p = 0.011$). In comparison to CNV, DNV had significantly lower mean 5th and 50th amplitude centiles ($p < 0.001$), while the mean 95th amplitude centile was higher ($p = 0.002$).

The aEEG amplitude centiles. There was a change of electrocerebral activity with both postnatal age and GA. The 5th amplitude centile correlated positively with both postnatal age ($r = 0.19$, $p = 0.004$) and GA ($r = 0.56$, $p < 0.001$). We found the opposite effect on the 95th amplitude centile: both postnatal age ($r = -0.14$, $p = 0.037$) and GA ($r = -0.19$, $p = 0.003$) had negative correlations with the 95th amplitude centiles.

We found no significant changes in the aEEG amplitude centiles during the first 5 d after birth. The 5th amplitude centile increased significantly between the 5th and 15th d (*t* test, $p = 0.001$) and between the 8th and 15th d (*t* test, $p = 0.021$). The changes in the aEEG amplitude centiles are shown in Figure 2.

The relationship between r_cSO_2*, FTOE, and postnatal age.* FTOE changed with postnatal age. r_cSO_2 decreased ($r = -0.27$, $p < 0.001$), whereas FTOE increased with postnatal age ($r = 0.32$, $p < 0.001$).

We found no changes in r_cSO_2 and FTOE during the first 5 d after birth. After the 5th d, there were significant changes in r_cSO_2 and FTOE. r_cSO_2 decreased from 79% on the 5th d to 76% on the 8th d and 70% on the 15th d. The differences between the 5th and 15th d and the 8th and 15th d were significant ($p < 0.001$ and $p = 0.007$, respectively). Although r_cSO_2 decreased, there was an increase in FTOE from 0.16 to 0.20 between the 5th and 8th d ($p = 0.03$) and from 0.20 to
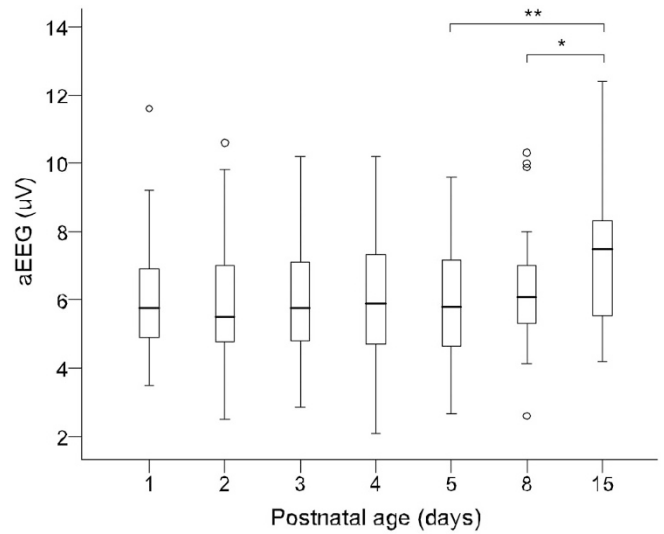
Figure 2. The relationship between the 5th aEEG amplitude centile and postnatal age. *$p < 0.05$; **$p < 0.01$.
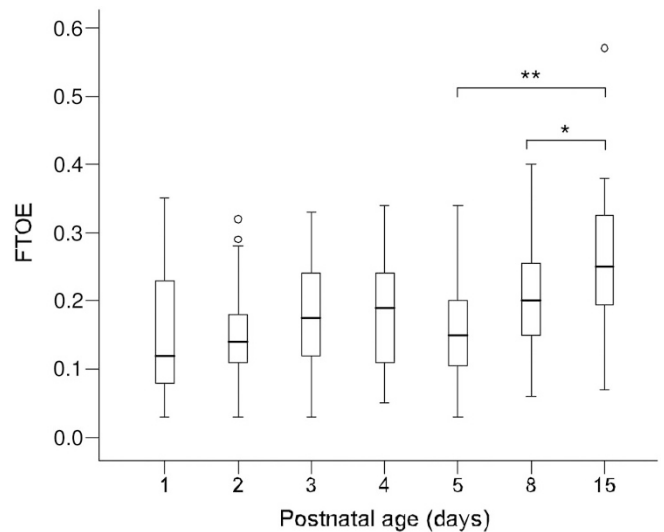
Figure 3. The relationship between FTOE and postnatal age. *$p < 0.01$; **$p < 0.001$.

0.26 between the 8th and 15th d ($p = 0.013$). The increase between the 5th and 15th d was highly significant ($p < 0.001$). The course of FTOE is shown in Figure 3.

The relationship between aEEG amplitude centiles and FTOE. The 5th and 50th aEEG amplitude centiles correlated positively with FTOE ($r = 0.26$, $p < 0.001$ and $r = 0.14$, $p = 0.035$, respectively). The 95th amplitude centile correlated negatively with FTOE ($r = -0.13$, $p = 0.042$).

The relationship between FTOE and the clinical variables.
Because several clinical conditions may interfere with cerebral oxygen delivery, we investigated whether these conditions confounded the relationships we found for FTOE and aEEG amplitude centiles. We checked blood pressure, persistent ductus ateriosus (PDA), ventilatory support, $Paco_2$, and Hb levels. There was no relationship between FTOE and blood pressure or $Paco_2$. We did, however, find a negative correlation between Hb levels and FTOE ($r = -0.30$, $p = 0.001$). FTOE was influenced by the mode of ventilation. We found that infants on low flow or infants without ventilatory support had higher FTOE compared with infants on nasal CPAP or artificial ventilation (0.22 *versus* 0.16, $p < 0.001$). The values of $tcSaO_2$ were significantly higher in infants on low flow or infants without ventilatory support compared with infants with CPAP (97% *versus* 94%, $p < 0.001$) and artificial ventilation (97% *versus* 91%, $p < 0.001$). There was no difference between infants on nasal CPAP or artificial ventilation. There was a slightly lower FTOE in case of a PDA during recording (0.17 *versus* 0.19, $p = 0.029$). The Hb levels were not different between the infants with and without a PDA.

Multivariate linear regression. Because individual variables are likely to be interdependent, we performed a multivariate linear regression analysis to examine the determinants of FTOE. The variables we entered into the model were aEEG amplitude centiles, postnatal age, Hb level, mode of ventilation, and PDA. The 5th aEEG amplitude centile ($\beta = 0.12$ [95% CI: 0.003 to 0.20], $p = 0.01$), 95th aEEG amplitude centile ($\beta = -0.002$ [95% CI: -0.003 to 0], $p = 0.022$), postnatal age ($\beta = 0.005$ [95% CI: 0.001 to 0.009], $p = 0.009$), and Hb level ($\beta = -0.011$ [95% CI: -0.021 to -0.001], $p = 0.030$) remained in the model, explaining 22.5% of the variance.

DISCUSSION

Our study demonstrated a clear relationship between electrocerebral activity and FTOE. We found increased FTOE with changing electrocerebral activity. Increase of the 5th aEEG amplitude centile, decrease of the 95th aEEG amplitude centile, and, consequently, a narrower bandwidth of the aEEG were associated with higher FTOE. This higher FTOE may indicate higher cerebral oxygen consumption.

Electrocerebral activity changed with increasing gestational and postnatal age. The 5th aEEG amplitude centile increased while the 95th amplitude centile decrease concurrently. We consider this narrower bandwidth of the aEEG to be a more mature background pattern. We observed the same maturational effects on aEEG with increasing postnatal age. From the 5th d onward, a larger proportion of aEEGs showed continuous normal voltage. The aEEG amplitude centiles also changed significantly after the 5th postnatal day. Several previous publications reported maturational effects of both postnatal and GA on electrocerebral activity (7,13,14). Mostly, these studies recorded aEEG at weekly intervals. Our study indicated that this change in electrocerebral activity generally took place in the second week after birth.

From the 5th postnatal day onward, the maturation of electrocerebral activity occurred simultaneously with an increase of FTOE, an observation we reported previously (15). It has been reported that increased cerebral oxygen consumption in case of increased metabolism is met by an increase of cerebral blood flow (16), the so-called neurovascular coupling. In that case, FTOE is expected to remain stable. Similar as Yoxall and Weindling (16), we found no increase of FTOE during the first week after birth. Instead, we found an increase of FTOE during the second week after birth, which was independent of Hb levels and more mature electrocerebral activity. We speculate that this higher FTOE is at least partly the result of increased oxygen consumption, due to increased metabolism. It is an established fact that metabolism in preterm infants nearly doubles after the first week after birth (17). Theoretically, the increase of FTOE could also be the result of impaired oxygen delivery due to decreased cerebral blood flow. In case of lower cerebral blood flow, however, we would expect a decrease in electrocerebral activity. Moreover, none of the infants were treated with inotropes, and their blood pressure was within the normal ranges. We found no relationship between FTOE and blood pressure. This suggests that within normal ranges of blood pressure, cerebral autoregulation is intact.

Independent of electrocerebral activity and postnatal age, we found an increase of FTOE with decreasing Hb concentration. If the Hb concentration decreases, the absolute amount of oxygen transported is decreasing. Within ranges of constant oxygen demand, this may lead to a higher extraction of oxygen (18,19). These results are in line with the study of Roche-Labarbe *et al.* (20). They found an increase in cerebral oxygen consumption during the first 6 wk after birth, which was related to a decrease of Hb over the same period. The infants in our study cohort were relatively healthy preterm infants. If an infant's clinical condition worsens, oxygen supply can become critical. Under such circumstances, maintaining the Hb level can become crucial in preserving oxygen supply to the brain, and thus preventing brain damage.

FTOE was influenced by the mode of ventilatory support. Infants that were artificially ventilated or treated with nasal CPAP during aEEG recordings had lower FTOE than infants that only required low flow or no support at all. This was, however, not independent of other factors such as aEEG amplitude centiles and postnatal age. Oxygen delivery to the brain was not impaired in infants without artificial ventilation or nasal CPAP, $tcSaO_2$ was even higher in infants on low flow *via* nasal canula. Therefore, in hemodynamically stable infants, cerebral oxygen delivery is not influenced by the severity of RDS and the mode of ventilation itself. This is in line with a previous study that compared cerebral oxygen delivery and oxygen extraction in preterm infants with and without RDS (12). If, however, respiratory failure is accompanied by circulatory insufficiency, this may lead to impaired cardiac output, and, consequently, to lower cerebral perfusion. Lower cerebral perfusion may lead to higher FTOE and to a change of electrocerebral activity.

A negative effect on electrocerebral activity was reported following the so-called "InSurE" procedure for the treatment

of RDS (21). This negative effect was attributed to the administration of opioids before intubation. With this opoid-induced change in electrocerebral activity, cerebral oxygen delivery and FTOE were constant, suggesting a decreased oxygen demand in case of decreased electrocerebral activity. Because none of the infants in our study received opioids, changes in electrocerebral activity in this study reflect differences in postnatal and GA.

We checked for other potentially confounding factors such as CO_2 level and PDA. Hypocarbia causes cerebral vasoconstriction that results in decreased cerebral blood flow. Decreased cerebral blood flow may result in increased FTOE. A recent study reported a negative correlation between transcutaneous P_{CO_2} and FTOE (22). By contrast, we found no correlation between FTOE and Pa_{CO_2} level. One of the differences was that we did take blood samples, either arterial or capillary, to measure Pa_{CO_2} level. The Pa_{CO_2} levels were within the normal ranges. It may well be possible that at lower CO_2 levels cerebral blood flow diminishes and that FTOE increases as a result. Wardle *et al.* (23) found an increase in FTOE with a decrease of Pa_{CO_2} levels. They found an effect of Pa_{CO_2} levels within infants. We did not perform repeated and combined measurements of Pa_{CO_2} levels with FTOE. Therefore, it is possible that we have missed temporal changes of FTOE in relation to Pa_{CO_2} levels. We did find a lower FTOE in case of a PDA during recording. Because several factors were likely to be interdependent, we performed a multivariate analysis. A PDA did not contribute to FTOE independently. Lower FTOE seems to be explained by a lower gestational and postnatal age in infants with a PDA. Infants with a lower GA had less mature electrocerebral activity, which was associated with lower FTOE. The difference in FTOE could not fully be explained by a difference in Hb levels.

In conclusion, this study demonstrated a tight relationship between electrocerebral activity and oxygen consumption. As electrocerebral activity matured, oxygen consumption increased. Other factors influencing oxygen consumption were postnatal age and Hb level. This combination of FTOE and electrocerebral activity may be a useful biomarker of brain function in high-risk infants. The combination of high FTOE and low electrocerebral activity may well reflect impairment of cerebral oxygen delivery or perfusion and may be an indication for clinicians to focus on preserving oxygen supply to the brain to limit brain damage. More research is needed to study the implications of this combined monitoring approach for treating infants during the neonatal period.

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