Brain Activity and Cerebral Oxygenation After Perinatal Arterial Ischemic Stroke Are Associated With Neurodevelopment

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Background and Purpose—In infants with perinatal arterial ischemic stroke (PAIS), early prognosis of neurodevelopmental outcome is important to adequately inform parents and caretakers. Early continuous neuromonitoring after PAIS may improve early prognosis. Our aim was to study early cerebral electrical activity and oxygenation measured by amplitude-integrated electroencephalography (aEEG) and near-infrared spectroscopy in term neonates with PAIS and relate these to the development of cerebral palsy and cognitive deficit.

Methods—aEEG patterns and regional cerebral oxygen saturation ($rScO_2$) levels of both hemispheres were studied for 120 hours from the first clinical symptoms of PAIS (ie, seizures) onward. Multivariable analyses were used to investigate the association between aEEG, near-infrared spectroscopy, clinical variables, and neurodevelopmental outcome.

Results—In 52 patients with PAIS (gestational age, 40.4±1.4 weeks; birth weight, 3282±479 g), median time to a continuous background pattern was longer in the ipsilesional compared with the contralesional hemisphere (13.5 versus 10.0 hours; $P<0.05$). $rScO_2$ decreased over time in both hemispheres but less in the ipsilesional one, resulting in a $rScO_2$ asymmetry ratio of 4.5% (interquartile range, −4.3% to 5.9%; $P<0.05$) between hemispheres from day 3 after symptoms onward. Both time to normal background pattern and asymmetry in $rScO_2$ were negatively affected by gestational age, size of the PAIS, use of antiepileptic drugs, and mechanical ventilation. After correction for size of the PAIS on magnetic resonance imaging, a slower recovery of background pattern on ipsilesional aEEG and increased $rScO_2$ asymmetry between hemispheres was related with an increased risk for cognitive deficit (<−1 SD) at a median of 24.0 (interquartile range, 18.4–24.4) months of age.

Conclusions—Recovery of background pattern on aEEG and cerebral oxygenation are both affected by PAIS and related to neurocognitive development. Both measurements may provide valuable early prognostic information. Additionally, monitoring cerebral activity and oxygenation may be useful in identifying infants eligible for early neuroprotective interventions and to detect early effects of these interventions. (***Stroke***. **2019;50:2668-2676. DOI: 10.1161/STROKEAHA.119.025346.**)

Key Words: brain injury ■ developmental disabilities ■ hemodynamic monitoring ■ neonate/newborn ■ neonatal intensive care ■ stroke

Perinatal arterial ischemic stroke (PAIS) is defined as an acute symptomatic insult in an arterial territory confirmed by neuroimaging that occurs in 1:2300 newborns.[1,2] Most frequently, neonates with PAIS present with seizures within the first days after birth.[3–5] PAIS can lead to severe morbidity, such as cerebral palsy (CP), epilepsy, cognitive, behavioral, and language impairments.[1,6]

Early prognosis is important to adequately inform parents and caretakers, as well as to initiate new early intervention strategies that aim for neuroprotection or neuroregeneration.[7] Early estimation of the prognosis is currently based on neuroimaging with magnetic resonance imaging (MRI) using diffusion-weighted imaging. However, neuroimaging with MRI is not always possible in neonates who are unstable. Besides,

use of early MRI mainly focuses on involvement of the corticospinal tracts, such as pre-Wallerian degeneration, to predict motor development, while neuroimaging predictors for cognitive outcome are far less established.[6,8,9] Furthermore, neuroimaging only provides useful predictive information at the time of scanning, while early installed continuous neuromonitoring after PAIS may improve early prognosis of neurodevelopmental outcome.

This study will focus on amplitude-integrated electroencephalography (aEEG) and near-infrared spectroscopy (NIRS), both noninvasive, continuous techniques to monitor cerebral activity and oxygenation in unstable neonates before neuroimaging can be performed in conditions such as hypoxic-ischemic encephalopathy.[10–12] aEEG patterns and NIRS have shown to be related to neurological outcome in several neonatal disorders.[10,12–17] Nevertheless, aEEG and NIRS monitoring are still not standard practice in PAIS in most centers across the world.[10,17] Therefore, we will investigate aEEG patterns and NIRS values during the first 5 days after clinical symptoms of PAIS and relate these to neurodevelopmental outcome. We hypothesize that early neuromonitoring after PAIS may improve early prediction of neurodevelopmental outcome.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Patients

This is an observational retrospective cohort study that included term neonates (>36 weeks of gestational age), who were admitted to the tertiary neonatal intensive care unit of the Wilhelmina Children's Hospital (Utrecht, the Netherlands) with suspected PAIS based on clinical seizures between January 2009 and March 2018. The diagnosis of PAIS was confirmed in all infants by neuroimaging with MRI including diffusion-weighted imaging. For this study, infants with aEEG or NIRS recordings available were selected. Antiepileptic drugs (AEDs) were administered per clinical protocol when neonates showed signs of clinical and aEEG confirmed seizures. The number of AEDs was noted. In the Netherlands, phenobarbital is first-line AED after neonatal seizures, whereas second-line AED was either midazolam or lidocaine.

Information on relevant clinical parameters was collected from the patient chart. Social-economic status was approximated based on postal code, provided by the "Social and Cultural Planning Agency" in the Netherlands.[18] Furthermore, using neonatal MRI, PAIS was classified based on size and site of the lesion. A lesion was labeled large when it affected the whole territory of the middle cerebral artery, medium when it affected the middle cerebral artery territory partially or the area of the anterior cerebral artery or posterior cerebral artery, or small when the lesion was defined as a cortical or perforator stroke based on our previous work.[6] Lesions were located anteriorly or posteriorly to the central sulcus or were classified as central when they involved the central sulcus, the deep gray matter, or the complete middle cerebral artery territory. The presence of bilateral lesions was also recorded.

Between July 2009 and April 2016, 27 infants were part of a safety and feasibility study and treated with 3×1000 IU recombinant human erythropoietin.[7] All parents signed consent for this study and these infants were monitored with aEEG and NIRS as part of the study protocol. After initiation of this trial, neuromonitoring with both NIRS and aEEG became part of standard clinical care for all infants with (suspected) PAIS. The research question as addressed in this study was not part of the initial trial, but performing this study was waived by the ethical committee of our hospital. Two infants were part of a randomized placebo-controlled trial that was recently initiated in our center studying the effect of darbepoetin after PAIS (DINOSAUR [Darbepoetin for Ischemic Neonatal Stroke to Augment Regeneration]; URL: https://www.clinicaltrials.gov; unique identifier: NCT03171818).

Main Analyses

Neuromonitoring included simultaneous, bilateral continuous assessment of regional cerebral oxygen saturation ($rScO_2$) and electrical activity, which became standard clinical practice for infants with suspected PAIS in our neonatal intensive care unit. Neuromonitoring is applied by the attending nursing staff as soon as possible after admission. To allow comparison of the patients, data were calibrated from the time of the first clinical symptoms (usually seizures). Recordings were used up till 5 days (120 hours) after onset of symptoms.

For data processing, SignalBase v.7.8.1 (University Medical Center Utrecht, the Netherlands) was used. The first 120 hours after onset of PAIS were divided into 20 epochs of 6 hours each. From each epoch, 1 hour of continuous data was randomly chosen as representative for this epoch, and data were checked for the absence of clinical and subclinical (suspected) seizures and artifacts. These periods were used for analyzing patterns of the aEEG and mean $rScO_2$ in both hemispheres.

Monitoring Brain Activity Using aEEG

The aEEG (BrainZ Monitor, BRM3; Natus CA, Seattle, WA) signal was recorded from 2 frontal and 2 parietal electrodes (F3-P3 and F4-P4), according to the international electroencephalography 10 to 20 classification.[10,19] The aEEG recordings in both hemispheres (ipsilesional and contralesional of the stroke) were scored on background pattern and sleep-wake cycling by an experienced neonatal aEEG reviewer (L.S.d.V.). Background pattern was divided into flat trace, burst suppression−, burst suppression+, discontinuous normal voltage, and continuous normal voltage, as described by Hellstrom-Westas et al.[16] In further analyses, continuous normal voltage is referred to as a normal background pattern. Sleep-wake cycling was described as being absent, imminent, or present, as reported by Osredkar et al.[20] In further analyses, present sleep-wake cycling is referred to as normal.

Monitoring Cerebral Oxygenation and Perfusion Using NIRS

Cerebral oxygenation was monitored by NIRS (INVOS 5100C; Medtronic, Minneapolis, MN) with bilateral sensors placed over the frontoparietal cortex (small adult SomaSensor SAFB-SM; Medtronic, Minneapolis, MN).[21] Simultaneously, noninvasive blood pressure, heart rate, and Sa_{O_2} were measured. Median values for each variable were calculated per epoch.

The mean percentage above or below the reference range for $rScO_2$ of 55% to 85%[22] was calculated for each epoch. To correct for interindividual baseline differences, the asymmetry index (%) between $rScO_2$ level at the ipsilesional and contralesional hemisphere was calculated: ([$rScO_2$ ipsilesional−$rScO_2$ contralesional]/$rScO_2$ contralesional)×100%. An asymmetry index in $rScO_2$ ($rScO_2$−asymmetry) of 0% indicates no difference between hemispheres. Positive values indicate higher $rScO_2$ levels in the ipsilesional hemisphere, whereas negative values indicate higher $rScO_2$ levels in the contralesional hemisphere.

Neurodevelopmental Outcome

Neurodevelopmental outcome was determined during routine follow-up between 15 and 25 months of age. Cognitive development was determined by using the developmental quotient of the Griffiths Mental Development Scale, calculated by using all subscale scores except locomotion or the Bayley Scales of Infant and Toddler Development, Third Edition, as described previously.[6] CP was classified as unilateral spastic CP by a pediatric physiotherapist and neonatal neurologist who were unaware of neuromonitoring data. Unfavorable outcome was defined as cognitive deficit (<−1 SD on

Griffiths Mental Development Scale or Bayley Scales of Infant and Toddler Development, Third Edition) or development of CP.

Statistical Analysis

IBM SPSS Statistics v25 (IBM Corp, Armonk, NY) and R 3.0.0 for Windows with the nlme package (The R Foundation of Statistical Computing; www.r-project.org) were used for statistical analysis. Nonparametric variables were log-transformed to achieve normal distribution. Patient characteristics were summarized as counts and percentages for categorical variables, means±SD for parametric data, and as median±interquartile ranges (IQRs) for nonparametric data. To test for differences between groups, χ^2 test, 1 sample *t* tests, paired sample *t* test, independent *t* tests, 1-way ANOVA, or the nonparametric variant were used. Linear and binary regression analyses were performed to test the association between variables. To assess the effect of time on $rScO_2$ asymmetry, a mixed model analysis was performed, which allows to control for the number of observations per patient. Linear, quadratic, and cubic functions were explored for obtaining the best fitting data. Binary logistic regression models for cognitive deficit were compared using Omnibus Tests of Model Coefficients where a baseline model with size of lesion was compared with models including neuromonitoring variables. Receiver operating characteristic curves were created using Prism GraphPad Software (version 7.04 for Windows; GraphPad Software, Inc) to determine sensitivity and specificity at various cutoffs per outcome parameter. Estimated *P*<0.05 was considered statistically significant.

Results

A total number of 62 patients with PAIS were initially eligible. However, 10 infants had to be excluded, because of concomitant syndromes (n=3), other severe brain abnormalities (n=4), cardiac abnormalities requiring surgery (n=2), or death in the neonatal period due to severe hypoxic-ischemic encephalopathy (n=1). Hence, we included 52 patients. aEEG data were available in 49 patients, NIRS data in 39 patients, and 36 infants had simultaneous aEEG and NIRS available. All patient characteristics are displayed in Table 1.

Amplitude-Integrated Electroencephalography

Figure 1 demonstrates aEEG patterns over time in both hemispheres. At 24 hours after clinical symptoms of PAIS, 57% of the recordings showed a continuous normal voltage in the ipsilesional hemisphere, whereas this was 65% in the contralesional hemisphere. At the end of day 5 after symptoms, 71% of the aEEG recordings showed full recovery for both background pattern and sleep-wake cycling in the ipsilesional and 78% in the contralesional hemisphere (Figure 1). Median time to recovery to normal background pattern was longer for the ipsilesional than for the contralesional hemisphere (13.5 [IQR, 0.0–42.2] versus 10.0 [IQR, 0.0–38.4] hours; *P*<0.03), and also time to a mature sleep-wake cycling was longer in the ipsilesional compared with the contralesional hemisphere (58.8 [IQR, 32.4–120.0] versus 54.5 [IQR, 32.4–93.2] hours; *P*<0.05). In all infants, time to recovery of the aEEG pattern was always longer in the ipsilesional hemisphere.

The effect of clinical parameters that are described in Table 1 on the aEEG pattern was assessed. The aEEG patterns per lesion size subtype are presented in Figures I and II in the online-only Data Supplement. Median time to a normal background pattern of the ipsilesional hemisphere was significantly longer in patients with large lesions compared with those with small lesions (59.3 [IQR, 16.8–88.3] versus 0.0

Table 1. Baseline Characteristics

Patient Characteristics	
Male, %	28 (54)
Gestational age, wk	40.4 (39.3–41.0)
Birth weight, g	3268 (2981–3567)
Perinatal asphyxia (%)*	7 (14)
Therapeutic hypothermia (%)†	2 (4)
Apgar score at 5 min	9 (7–10)
Hypoglycemia <2.0 mmol/L (%)	9 (21)
First clinical symptoms of seizures (hours after birth)	24.0 (10.5–48.0)
Mechanical ventilation	12 (23)
Left-sided PAIS	31 (60)
aEEG	
Duration before start monitoring after seizures, h	11.4 (4.9–42.1)
Total duration monitoring, h	92.7 (66.7–115.1)
NIRS	
Duration before start monitoring after seizures, h	17.7 (5.8–51.4)
Total duration monitoring, h	66.8 (50.8–92.6)
No. of AEDs	
0–1	32 (62)
>1	20 (38)
Size of PAIS	
Small	18 (35)
Medium	25 (48)
Large	9 (17)
Artery involved	
MCA	39 (75)
PCA	4 (8)
Perforator stroke	8 (15)
PICA	1 (2)
Erythropoietin	
Safety and feasibility study	27
DINOSAUR study	2
None	23

Gestational age and birth weight are represented as mean (SD), other data as n (%) or median (IQR) where applicable. AED, antiepileptic drug; aEEG, amplitude-integrated electroencephalography; BE, base deficit; DINOSAUR, Darbepoetin for Ischemic Neonatal Stroke to Augment Regeneration; IQR, interquartile range; MCA, middle cerebral artery; NIRS, near-infrared spectroscopy; PAIS, perinatal arterial ischemic stroke; PCA, posterior cerebral artery; and PICA, posterior inferior cerebellar artery.

*Perinatal asphyxia was defined as an Apgar score ≤5 at 5 min or metabolic acidosis (cord pH <7.0 or BE ≤−16 mmol/L).

†Hypothermia was applied when criteria for cooling were met including signs of encephalopathy within 6 h after birth.

[0.0– 31.7] hours; *P*<0.03). Lower gestational age, >1 AED, and mechanical ventilation all resulted in a longer time to normal background pattern of both hemispheres (all *P*<0.03). Time to normal sleep-wake cycling was not related to clinical
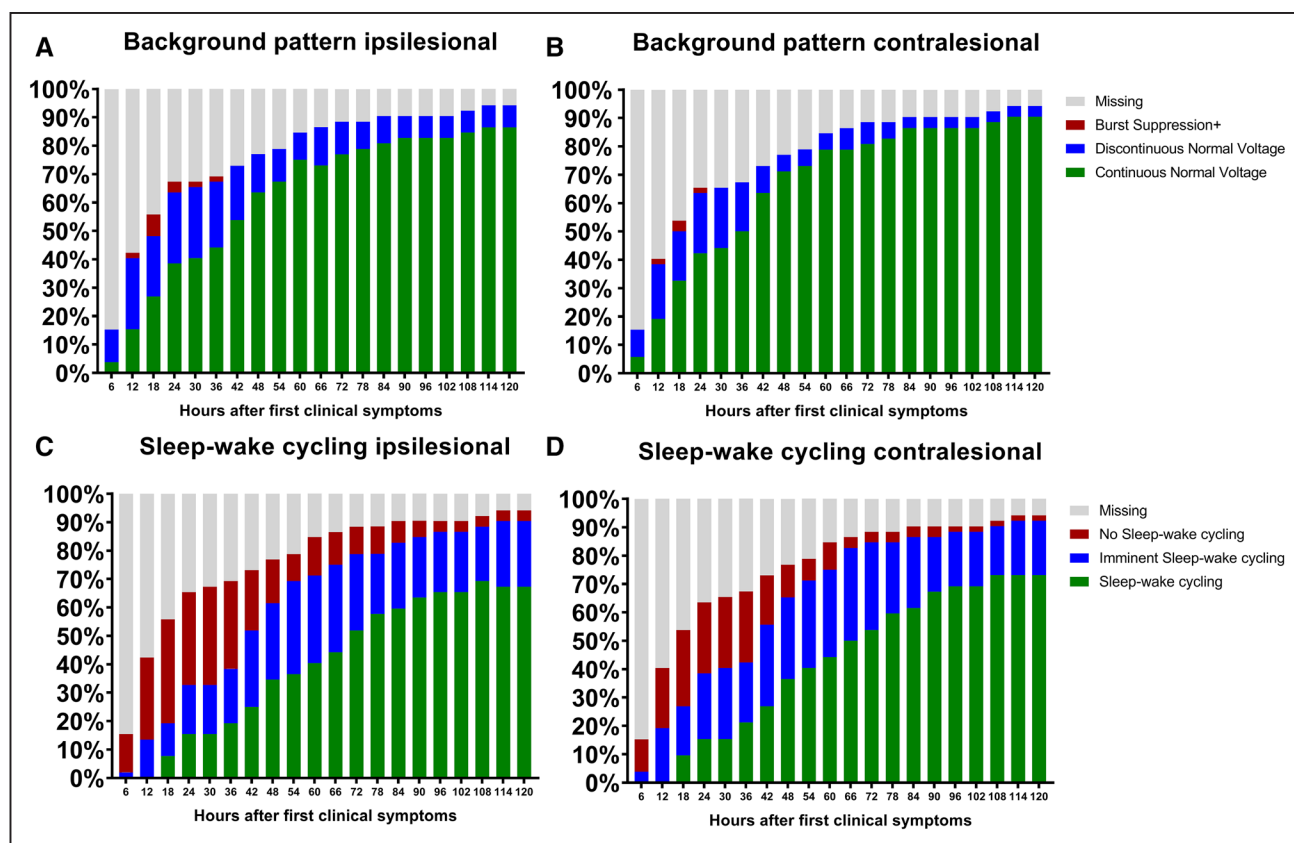
Figure 1. Amplitude-integrated electroencephalography (aEEG) patterns over time in the ipsilesional and contralesional hemispheres. aEEG patterns are classified based on background pattern (**A** and **B**) and sleep-wake cycling (**C** and **D**) in periods of 6 h starting from first clinical symptoms.

parameters. After multivariable analyses, gestational age (coefficient, −12.4; 95% CI, −18.3 to −6.5), >1 AED (coefficient, 19.8; 95% CI, 0.3–39.3), and mechanical ventilation (coefficient, 22.0; 95% CI, 0.2–43.8) were significantly and independently associated with time to normal background pattern.

Near-Infrared Spectroscopy

Mean $rScO_2$ values over time are presented in Figure 2. Overall, the mean level of $rScO_2$ was higher on the ipsilesional side (72.8±10.8%) compared with the contralesional one (69.7±10.3%; $P<0.001$). This resulted in a median $rScO_2$ asymmetry of 4.2% (IQR, −5.0% to 15.4%). From day 3 after clinical symptoms onward, there was a significant difference in $rScO_2$ levels between ipsilesional and contralesional hemisphere (Figure 2). The variables gestational age, time in days, size of the lesion, birth asphyxia, use of AED, and mechanical ventilation were all associated with an increased $rScO_2$ asymmetry ($P<0.001$, $P<0.003$, $P<0.001$, $P<0.02$, $P<0.01$, and $P<0.001$, respectively). The side and location of the lesion, presence of bilateral lesions, or erythropoietin administration did not affect $rScO_2$ asymmetry. After mixed model analyses, the best model to explain variance in $rScO_2$ asymmetry included large (versus small) size of the lesion (coefficient, 16.9; 95% CI, 9.8–23.9), >1 AED (coefficient, 5.6; 95% CI, 0.2–11.0), and time in days (coefficient, 2.9; 95% CI, 1.4–4.3). $rScO_2$ asymmetry data were normalized using log-transformation, but this did not affect the model and are, therefore, not presented here.

Reference Values of $rScO_2$

The $rScO_2$ of the ipsilesional hemisphere was on average 12.8% of the time above the upper reference value of 85%, against 6.3% on the contralesional side ($P<0.001$). On the contrary, the contralesional side was on average 8.5% of the time below the lower reference value of 55%, against 5.4% of the ipsilesional side ($P<0.03$).

Neurodevelopmental Outcome

Neurodevelopmental outcome data were available for 44 infants (85%); 2 infants were lost to follow-up, and 6 others were not yet 15 months of age. Of these, 25 infants (57%) were tested using the Bayley Scales of Infant and Toddler Development, Third Edition, and 19 infants (43%) were tested with the Griffiths Mental Development Scale. At a median age of 24.0 (IQR, 18.5–24.4) months, 12 infants had adverse outcomes: 9 infants (17%) developed CP, and 8 infants (15%) had an impaired cognitive outcome.

Large (versus small) lesions were associated with increased risk of an adverse outcome, including CP (odds ratio [OR], 90.0; 95% CI, 4.8–1683.9) and cognitive deficit (OR, 20.0; 95% CI, 1.6–248.0). Other clinical variables, including erythropoietin or social-economic status, were not significantly related to neurodevelopmental outcome.

aEEG in Relation to Outcome

In patients with adverse outcome (both CP and cognitive deficit), the time to continuous normal voltage was longer
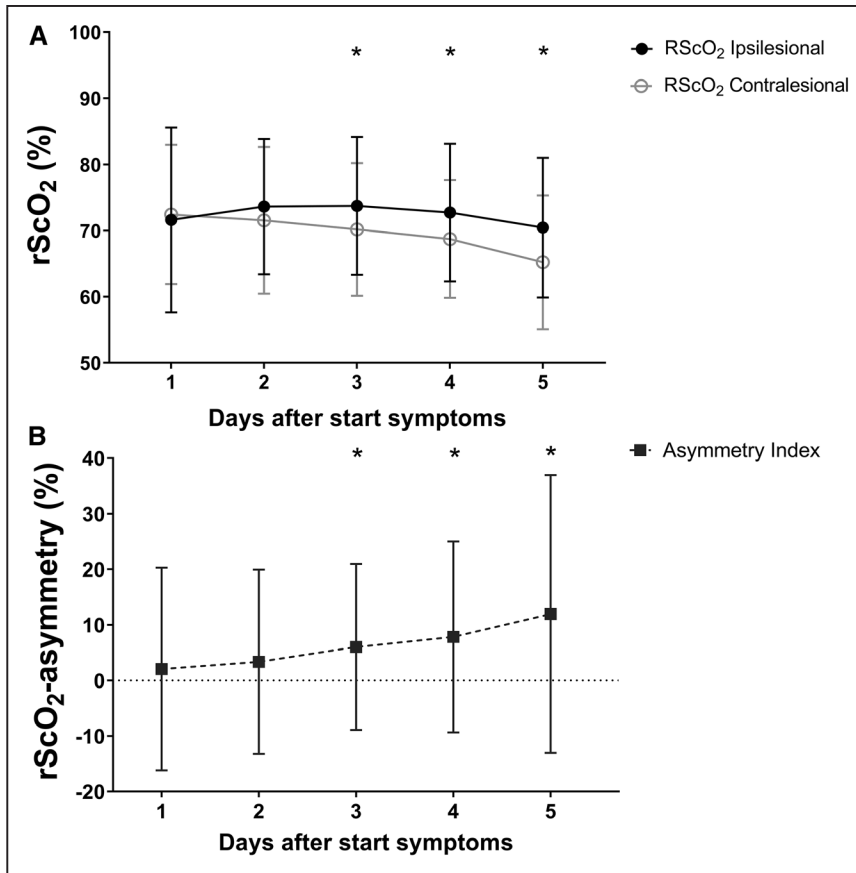
Figure 2. Near-infrared spectroscopy (NIRS) parameters in ipsilesional and contralesional hemispheres. Regional cerebral oxygen saturation (rScO$_2$; **A**) and rScO$_2$ asymmetry (**B**) on NIRS over first 5 d after clinical symptoms of perinatal arterial ischemic stroke. *Significant difference between hemispheres. rScO$_2$ asymmetry is the asymmetry index (%) between rScO$_2$-level at the ipsilesional and contralesional hemisphere.

in the ipsilesional hemisphere compared with patients with a normal outcome (Table 2). Time to continuous normal voltage in the contralesional hemisphere was also longer in patients who developed cognitive deficits compared with those with normal cognition (Table 2). Time to normal background pattern of the ipsilesional hemisphere was used for receiver operating characteristic analyses to predict CP and cognitive deficit using optimal cutoffs (Figure 3).

NIRS in Relation to Outcome

The rScO$_2$ in the ipsilesional hemisphere was significantly higher in patients with an unfavorable outcome compared with those with a favorable outcome, while rScO$_2$ values at the

Table 2. Association of aEEG Parameters to Neurodevelopmental Outcome

	Unfavorable Outcome		CP		Cognitive Deficit	
Outcome	No	Yes	No	Yes	No	Yes
Time to CNV ipsilesional, h*	17.6 (20.6)†	51.7 (46.4)†	19.6 (27.0)†	55.6 (41.1)†	19.4 (23.8)†	60.8 (48.1)†
Time to CNV contralesional, h*	16.1 (19.6)	40.8 (43.1)	18.3 (26.4)	41.0 (36.8)	16.6 (22.1)†	51.0 (43.1)†
Time to SWC ipsilesional, h*	61.8 (36.8)	79.4 (50.4)	59.8 (39.6)†	92.6 (38.9)†	64.6 (38.5)	76.4 (53.5)
Time to SWC contralesional, h*	59.6 (35.1)	72.6 (49.5)	57.8 (38.1)	83.5 (40.5)	62.4 (37.1)	67.2 (51.5)
rScO$_2$ ipsilesional (%)*	70.2 (9.6)†	78.5 (11.9)†	69.9 (9.4)†	80.4 (11.6)†	71.3 (9.6)†	79.4 (13.7)†
rScO$_2$ contralesional (%)	69.1 (10.8)	70.3 (10.7)	69.4 (10.7)	69.8 (11.0)	69.9 (10.5)	68.3 (11.7)
rScO$_2$ asymmetry (%)*	2.8 (13.8)†	15.8 (22.7)†	2.5 (13.5)†	17.8 (23.1)†	3.2 (13.8)†	22.0 (24.4)†
rScO$_2$ ipsilesional day 3 (%)	72.0 (9.9)†	79.0 (11.1)†	71.5 (9.9)†	81.5 (9.8)†	72.9 (9.7)†	80.1 (12.6)†
rScO$_2$ contralesional day 3 (%)	68.7 (10.9)	72.7 (10.0)	69.1 (10.7)	72.2 (10.5)	69.9 (10.7)	70.9 (10.9)
rScO$_2$ asymmetry day 3 (%)	4.2 (12.7)†	13.3 (17.0)†	3.7 (12.4)†	15.5 (16.8)†	4.3 (12.5)†	18.9 (17.5)†

Data are presented as mean (SD). Time to an SWC: time to mature sleep-wake cycling on aEEG. Time to CNV: time to a continuous normal voltage background pattern on aEEG. aEEG indicates amplitude-integrated electroencephalography; CNV, continuous normal voltage; CP, cerebral palsy; rScO$_2$, regional cerebral oxygen saturation; and SWC, sleep-wake cycling.

*Non-normally distributed data were tested by nonparametric tests.

†Significant difference between subdivisions of that outcome domain (*P*<0.05).
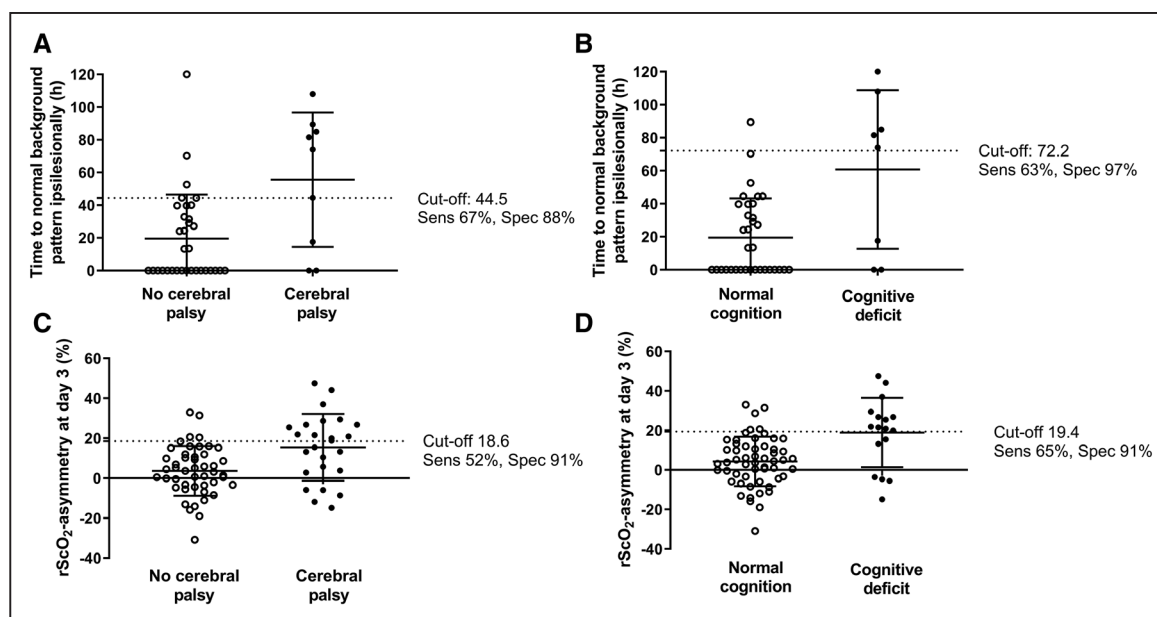
Figure 3. Cutoff values for amplitude-integrated electroencephalography (aEEG) and near-infrared spectroscopy parameters to predict adverse neurodevelopmental outcome. Time to a normal background pattern (continuous normal voltage) on aEEG and regional cerebral oxygen saturation ($rScO_2$) asymmetry on day 3 predicted cerebral palsy (**A–C**) and cognitive deficit (**B–D**). Sens indicates sensitivity; and Spec, specificity.

contralesional hemisphere did not relate to outcome (Table 2). $rScO_2$ asymmetry was higher in patients who had an adverse outcome compared with those with normal development. Mixed model analyses revealed that time (day) after PAIS did not add to the relation of NIRS parameters and outcome: ipsilesional $rScO_2$ and $rScO_2$ asymmetry were associated with CP and cognitive deficit on all 5 days after PAIS symptoms (Table 2; Figure 4). Only on day 2, ipsilesional $rScO_2$ did not differ between infants with a good and adverse cognitive outcome (Figure 4).

As ipsilesional and contralesional $rScO_2$ values became different from day 3 onward after PAIS symptoms, $rScO_2$ asymmetry at day 3 was used to calculate optimal cutoffs for the prediction of CP and cognitive deficit (Figure 3).

Multivariable Analyses
Multivariable analyses revealed that after correction for size of the lesion, both time to normal background pattern on aEEG and $rScO_2$ asymmetry on NIRS were still associated with cognitive outcome. Increased time to normal background pattern of the ipsilesional hemisphere (per 24 hours: OR, 1.9; 95% CI, 1.0–3.6; P=0.05; Nagelkerke R^2=0.39) and $rScO_2$ asymmetry at day 3 (per 10%: OR, 1.8; 95% CI, 1.1–3.0; Nagelkerke R^2=0.58) were still associated with cognitive deficit after correction for size of the lesion. Both models were significantly better associated with cognition than size of lesion alone (large versus small lesion: OR, 20.0; 95% CI, 1.6–248.0; Nagelkerke R^2=0.25; P=0.04 and P=0.02, respectively). A model combining neuromonitoring data revealed that both time to normal background pattern (per 24 hours: OR, 9.6; 95% CI, 1.9–49.6) and $rScO_2$ symmetry at day 3 (per 10%: OR, 7.9; 95% CI, 1.3–45.9) were independently related to cognitive deficit when correcting for size of lesion (Nagelkerke R^2=0.89). This model was significantly better than a model with size of lesion alone (P<0.0001).

Discussion
In this retrospective cohort study, aEEG and NIRS measurements were studied in term neonates that presented with clinical seizures due to PAIS. To the best of our knowledge, this is the first study that describes the course of aEEG and NIRS parameters in both hemispheres during the first 5 days after clinical symptoms due to PAIS. Differences in cerebral activity and oxygenation were found between the ipsilesional and contralesional hemisphere, which were also affected by size of PAIS, gestational age, use of AEDs, and mechanical ventilation. Moreover, aEEG and NIRS values were found to be associated with neurocognitive development at 15 to 24 months of age, even after correction for size of the lesion.

The $rScO_2$ decreased during the first 5 days after clinical symptoms of PAIS in both hemispheres but less in the ipsilesional than in the contralesional hemisphere. This was also reflected by the $rScO_2$ asymmetry, resulting in a significant $rScO_2$ asymmetry from day 3 onward. A relatively low $rScO_2$ of the ipsilesional hemisphere can be explained by a state of hypoperfusion in the first few hours after PAIS.[23] A subsequent relative rise of $rScO_2$ of the ipsilesional hemisphere can be due to hyperperfusion (due to luxury perfusion).[23,24] This state of luxury perfusion is likely to affect both hemispheres, in line with abnormal brain activity as measured by aEEG bilaterally. Alternatively, high $rScO_2$ can also be due to reduced oxygen consumption by the damaged brain tissue of the ipsilesional hemisphere. De Vis et al[25] demonstrated higher $rScO_2$ values accompanied by hypoperfusion, as measured by NIRS and arterial spin labeling on days 5 to 6, in the ipsilesional hemisphere in 3 of 4 cases with PAIS. We hypothesize that the persisting relatively high $rScO_2$ ipsilesional is explained by initial luxury perfusion, gradually progressing to a normal/low perfusion state accompanied by decreased O_2 consumption. The contralesional $rScO_2$ was initially as high as ipsilesional, reflecting
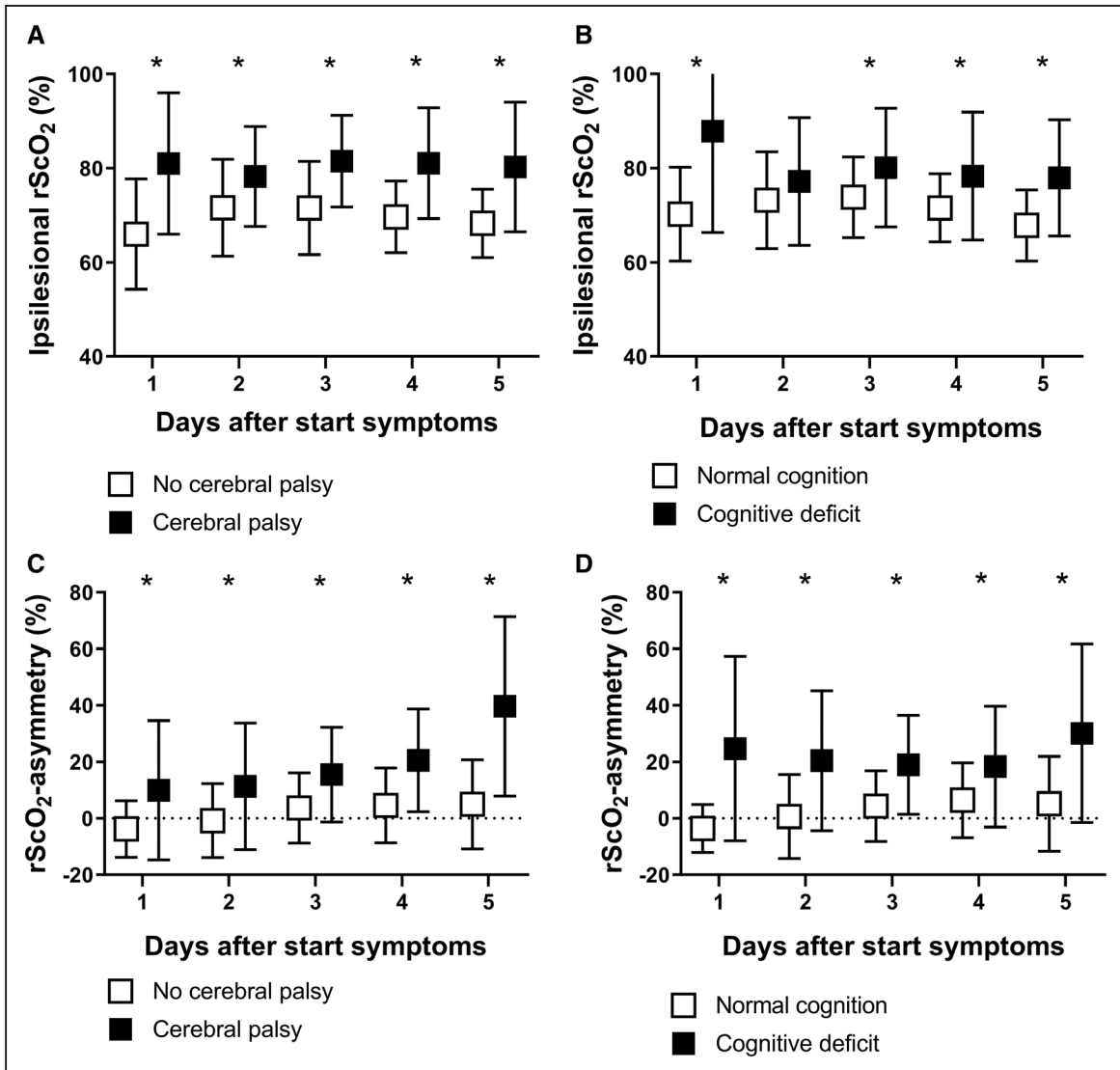
Figure 4. Near-infrared spectroscopy (NIRS) parameters in the first 5 d after clinical symptoms of perinatal arterial ischemic stroke in relation to neurodevelopmental outcome. Ipsilesional regional cerebral oxygen saturation ($rScO_2$) is increased in infants with cerebral palsy (CP; **A**) and cognitive deficit (**B**). Asymmetry ratio of $rScO_2$ increases in infants with CP (**C**) and cognitive deficit (**D**).

the same initial luxury perfusion state of the brain. However, subsequent normalization of perfusion at the ipsilateral hemisphere was accompanied by rather stable O_2 consumption during days 0 to 5. Impaired autoregulation of the brain after injury could be a plausible explanation for this phenomenon and would be an interesting aspect to explore in future studies.

In healthy term infants, normal background pattern and sleep-wake cycling is present in 99% and 96% of infants directly or within a few hours after birth.[26] Overall in our cohort, PAIS led to a disruption of background pattern and sleep-wake cycling in both hemispheres, with >40% of the infants not having a normal background pattern within 1 day after the onset of the first clinical symptoms of PAIS. Additionally, only 59% showed mature sleep-wake cycling 72 hours after the first symptoms. Several studies reported an impaired sleep-wake cycling and a suppressed background pattern in infants with PAIS or clinical seizures.[27,28] In line with our results, cerebral activity was more severely affected in the ipsilesional hemisphere, especially after large PAIS.[28]

Cerebral activity and oxygenation were not only negatively influenced by PAIS and size of the lesion but also by administration of AEDs and mechanical ventilation. Seizures and the use of AED medication, in particular midazolam, are known to be associated with apneas and the need for mechanical ventilation.[29] The effect of AED on background pattern is known to be more pronounced in infants with more severe brain injury. This explains the effect of AEDs and mechanical ventilation on AR-$rScO_2$ asymmetry, as the damaged ipsilesional hemisphere responded more to sedatives than the contralesional hemisphere.[30] In this study, the use of AEDs and use of sedation during mechanical ventilation are clinical factors associated with neuromonitoring that could be managed during neonatal intensive care unit admission. Although both will have an initial negative affect on background activity, more rapid control of convulsions will ultimately improve recovery of background activity. However, our results warrant critical evaluation of the use of AEDs and sedation after PAIS because these might negatively influence neurodevelopmental outcome.

Neuroimaging using MRI is the gold standard to diagnose PAIS, and various studies have demonstrated its predictive ability for neurodevelopmental outcome.[6] Our study confirms that size of the lesion on neonatal MRI is indeed strongly related to cognitive and motor outcome at 15 to 25 months of age. In univariate analyses, unfavorable outcome was associated with increased time to normal background pattern and increased $rScO_2$ in the ipsilesional hemisphere, in line with several other studies in other neonatal populations.[12–17] Our group previously reported that combining aEEG and NIRS parameters in infants with hypoxic-ischemic encephalopathy in a multivariable model was associated with neurological outcome,[12,17] which is comparable to our multivariable model. After correction for size of the lesion, time to normal background pattern at the ipsilesional hemisphere and $rScO_2$ asymmetry were still independently associated with impaired cognition. MRI predictors for cognitive deficit after PAIS usually include size or location of the lesion, but more specific regions of interest on MRI have not been well established.[6,9] Our study is the first to demonstrate that NIRS and aEEG may add to prediction of cognitive outcome. It also provides targets for potential new therapies to improve cognition, for example, neuroprotective agents at times of increased $rScO_2$ asymmetry to protect the brain from O_2 radicals produced after luxury perfusion.

The study cohort consisted of patients who presented with clinical symptoms of PAIS, mostly hemiconvulsions or apneas, thereby excluding those without any evident clinical symptoms, and mostly likely those with smaller infarcts.[31] This reduced the number of eligible infants and thereby the statistical power of our study. However, the advantage is that our registration data are homogeneous because all patients presented with symptoms of PAIS, allowing comparison of neuromonitoring data over time. Because the exact moment of PAIS is unknown, onset of seizures was used as the start of our study period, but some infants may exhibit seizures after PAIS later than others. Although this may have influenced our results, timing of seizure onset after perinatal stroke needs to be elucidated in future studies.

Neuromonitoring data were collected as part of standard clinical care, and recordings were usually started several hours after onset of clinical symptoms, because most infants were outborn. This resulted in many missing data between symptoms and start of the recording during the first day after symptoms. Patients with smaller strokes often showed a normal background pattern on aEEG at the start of the recording, so the exact effect of PAIS on the background pattern during the first hours is unknown in these infants. Consequently, the average time to normal background pattern reported here is still conservative, however does reflect standard clinical practice after PAIS.

For this study, outcome parameters such as development of CP and cognitive deficit were collected between 15 and 25 months of age. Follow-up studies are continued till school age to see whether neurological outcome remains stable over time, or other disabilities present later in life (eg, attention disorders), and how neuromonitoring tools relate to these.

Conclusions

PAIS affects cerebral activity and oxygenation in both hemispheres. As neuromonitoring parameters are related

to neurodevelopmental outcome, these results illustrate that aEEG and NIRS monitoring may provide useful information for early prognosis of PAIS, especially of cognition. Before drawing firm conclusions, more prospective research is necessary with a larger study population and with more complete registrations during several days. However, continuous neuromonitoring is a promising way to optimize care. Because of the prognostic value, aEEG and NIRS could potentially be used to monitor the effect of early interventions.

Disclosures

Dr Groenendaal discloses to have received modest compensation as an expert witness in malpractice cases. The other authors report no conflicts.

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