Amplitude-Integrated Electroencephalography for Early Recognition of Brain Injury in Neonates with Critical Congenital Heart Disease

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Objective To study perioperative amplitude-integrated electroencephalography (aEEG) as an early marker for new brain injury in neonates requiring cardiac surgery for critical congenital heart disease (CHD).

Study design This retrospective observational cohort study investigated 76 neonates with critical CHD who underwent neonatal surgery. Perioperative aEEG recordings were evaluated for background pattern (BGP), sleep-wake cycling (SWC), and ictal discharges. Spontaneous activity transient (SAT) rate, inter-SAT interval (ISI), and percentage of time with an amplitude <5 μV were calculated. Routinely obtained preoperative and postoperative magnetic resonance imaging of the brain were reviewed for brain injury (moderate-severe white matter injury, stroke, intraparenchymal hemorrhage, or cerebral sinovenous thrombosis).

Results Preoperatively, none of the neonates showed an abnormal BGP (burst suppression or worse) or ictal discharges. Postoperatively, abnormal BGP was seen in 18 neonates (24%; 95% CI, 14%-33%) and ictal discharges was seen in 13 neonates (17%; 95% CI, 8%-26%). Abnormal BGP and ictal discharges were more frequent in neonates with new postoperative brain injury ($P = .08$ and .01, respectively). Abnormal brain activity (ie, abnormal BGP or ictal discharges) was the single risk factor associated with new postoperative brain injury in multivariable logistic regression analysis (OR, 4.0; 95% CI, 1.3-12.3; $P = .02$). Postoperative SAT rate, ISI, or time <5 μV were not associated with new brain injury.

Conclusion Abnormal brain activity is an early, bedside marker of new brain injury in neonates undergoing cardiac surgery. Not only ictal discharges, but also abnormal BGP, should be considered a clear sign of underlying brain pathology. *(J Pediatr 2018;■■:■■-■■).*

Neonates undergoing open-heart surgery early in life for critical congenital heart disease (CHD) are at increased risk for brain injury and subsequent impaired neurodevelopment.[1-3] Although time of diagnosis, type of CHD, and blood pressure-related problems have been identified as risk factors for brain injury,[4,5] it remains difficult to identify neonates with the highest risk for developing brain injury at an early stage.

Magnetic resonance imaging (MRI) is the most accurate tool for diagnosing brain injury in neonates with CHD.[6] However, MRI is discontinuous and not always feasible in critically ill neonates. Therefore, continuous bedside neuromonitoring techniques such as amplitude-integrated electroencephalography (aEEG) are increasingly used to closely monitor brain activity around neonatal cardiac surgery. aEEG is derived from (standard) electroencephalography (EEG) and has multiple characteristics for the assessment of brain activity.

Several studies have shown the relationship between abnormal neonatal aEEG characteristics and subsequent impaired neurodevelopment in CHD survivors.[7,8] However, studies reviewing the association between brain activity and brain injury are lacking. If aEEG characteristics can be identified as markers of neonatal brain injury, this may provide opportunities for interventions and optimization of care in neonates requiring cardiac surgery.

aEEG	Amplitude-integrated electroencephalography	CNV	Continuous normal voltage
BGP	Background pattern	CPB	Cardiopulmonary bypass
BS–	Sparse burst suppression	DNV	Discontinuous normal voltage
BS+	Dense burst suppression	EEG	Electroencephalography
BVP	Biventricular physiology without aortic arch obstruction	FT	Flat trace
BVP-AO	Biventricular physiology with aortic arch obstruction	ISI	Inter-SAT interval
CHD	Congenital heart disease	SAT	Spontaneous activity transient
		SVP	Single-ventricle physiology
		SWC	Sleep-wake cycling

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This study aimed to describe perioperative aEEG-measured brain activity in neonates undergoing neonatal open-heart surgery for critical CHD, as evaluated by both qualitative and quantitative (event- and amplitude-based) measures, in relation to preoperative and postoperative MRI-measured moderate-severe brain injury. The secondary aim was to evaluate early postnatal aEEG characteristics in relation to preoperative brain injury in a subgroup of neonates with critical CHD.

Methods

This was a retrospective observational cohort study including two cohorts of neonates with critical CHD (defined as biventricular physiology with or without aortic arch obstruction [BVP-AO or BVP, respectively], or single ventricle physiology [SVP]), who underwent neonatal open-heart surgery with the use of cardiopulmonary bypass (CPB), and were born between 2009 and 2017 at the Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands. The surgical treatment of CHD did not change during this period. The first cohort was born between 2009 and 2012 (BVP-AO and SVP), and perioperative aEEG monitoring and MRI were performed for research purposes. This cohort consisted of 37 neonates; however, 2 did not have perioperative aEEG recordings and thus were excluded. The local Medical Ethical Committee approved this study, and parental informed consent was obtained. The second cohort was born between February 2016 and June 2017 (BVP, BVP-AO, and SVP), and aEEG monitoring and MRI scans were performed clinically in both the early postnatal and perioperative periods. The Medical Ethics Committee provided permission to use the routinely obtained aEEG and MRI data for research purposes. Neonates with a gestational age ≤36 weeks, confirmed genetic disorders, or multiple congenital anomalies were excluded from this study.

In both cohorts, aEEG monitoring was started 6 hours before surgery and continued during surgery until at least 48 hours after surgery. In the second cohort, aEEG monitoring was also started as soon as possible after birth and continued for at least 36 hours. For all neonates, an aEEG monitor (BrainZ; Natus, Seattle, Washington) with a sampling rate of 256 Hz was used. Four subcutaneous needle electrodes (F4-P4 and F3-P3) were applied with a central reference electrode (Fz) measuring the impedance. aEEG recordings were qualitatively evaluated for background pattern (BGP), sleep-wake-cycling (SWC), and (electroencephalographic) ictal discharges by 3 experts who were blinded to the neonatal clinical course and MRI results. BGP was classified as continuous normal voltage (CNV), discontinuous normal voltage (DNV), dense burst suppression (BS+), sparse burst suppression (BS-), continuous low voltage, or flat trace (FT).[9] CNV and also DNV were considered normal BGPs, because even healthy term neonates show discontinuous activity during quiet sleep,[10] and also because aEEG brain activity might be suppressed by drugs such as morphine and midazolam.[11,12] Administration of these drugs is standard clinical care during and after cardiac surgery in neonates with CHD. BS+, BS-, continuous low voltage, and FT were considered abnormal BGPs. SWC was graded as absent, imminent (immature), or normal. Ictal discharges were classified as single, repetitive, or status epilepticus. Examples of BGP, SWC, and ictal discharges have been presented by Stolwijk et al.[13]

In-house developed software (SignalBase version 8.5.6; University Medical Center Utrecht, Utrecht, The Netherlands) was used to analyze the raw EEG and aEEG data. One epoch of 1 hour was selected the night before surgery. During CPB, an epoch of 30 minutes was selected at the moment of lowest rectal temperature. After surgery, 9 epochs of 1 hour were selected: 1-2 hours, 4-6 hours, 10-12 hours, 16-18 hours, 22-24 hours, 34-36 hours, 46-48 hours, 58-60 hours (if available), and 70-72 hours (if available). To study our secondary aim, epochs of 1 hour were selected at 5 postnatal time points: 10-12 hours, 16-18 hours, 22-24 hours, 34-36 hours, and 46-48 hours (if available). Epoch selection was done manually to avoid artifacts, caretaking events, and periods with high impedance. For all epochs, SAT rate (ie, number of SATs per minute) and inter-SAT interval (ISI; ie, time between SATs, in seconds per minute) were derived from the raw EEG data. The left and right hemispheres were analyzed separately. In addition, the percentage of time with an amplitude <5 μV was calculated. Examples of event-based (SAT and ISI) and amplitude-based (time <5 μV) measures have been provided by Benders et al.[14]

Neonates underwent MRI before (within the first week of life) and after surgery (approximately after 7 days) using a 1.5-T MRI system in 2009-2012 (Gyroscan ACS-NT; Philips Medical Systems, Best, The Netherlands) or a 3.0-T MRI system in 2016-2017 (Achieva; Philips Medical Systems). Neonates who required mechanical ventilation at the time of MRI received continuous sedation. Neonates without mechanical ventilation were fed, swaddled in a vacuum cushion, and, if necessary, sedated with oral chloral hydrate (single dose of 50-60 mg/kg). Both the 1.5-T and 3-T MRI protocols included 3D T1-weighted, T2-weighted, axial diffusion-weighted, and susceptibility-weighted sequences, as well as 3D venography. All MRI scans were reviewed by 2 independent researchers with experience in neonatal neurology, blinded to the patient's clinical information. White matter injury was graded as absent, mild, moderate, or severe, based on the number and size of the lesions.[5] Moderate-severe brain injury was defined as either moderate-severe white matter injury, stroke, intraparenchymal hemorrhage (involving >5% of a hemisphere) or cerebral sinovenous thrombosis. Brain injury was defined as moderate-severe brain injury.

Statistical Analyses

All statistical analyses were performed using SPSS version 21 (IBM, Armonk, New York). All variables were checked for normality of distribution (using a q-q plot) and homogeneity of variance (using the Levene test). Left-right differences were tested with the Wilcoxon signed-rank test. Poisson 95% CIs were calculated for incidences. Logistic regression analysis and the Fisher exact test were used to analyze the association of clinical factors with qualitative aEEG measures. Linear regression analysis and the Mann-Whitney *U* test were used to analyze

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the association of clinical factors with quantitative aEEG measures. Because all neonates received morphine and midazolam after surgery, cumulative dosages of morphine (mg/kg) and midazolam (mg/kg) were calculated for each of the postoperative time points. Postoperatively, the model always included gestational age and cohort and tested the following independently: duration of CPB, lowest rectal temperature, open sternum, repeat thoracotomy, arrhythmias, culture-proven infection, morphine dosage, and midazolam dosage. Preoperatively, the model always included gestational age, and the following variables were tested independently: sex, postnatal diagnosis, SVP, morphine administration, and midazolam administration. For the comparison of neonates with and without new postoperative brain injury, BGP was classified as 0-5 (with FT as 0 and CNV as 5). Multivariable logistic regression analysis was performed to examine the association between aEEG measures and new brain injury, and always included CHD category, gestational age, and total midazolam dose. aEEG variables tested included duration of FT, not reaching CNV in <24 hours, postoperative abnormal BGP <48 hours, ictal discharges, SAT rate, ISI, and time <5 μV. Positive and negative predictive value were calculated for abnormal brain activity (ie, abnormal BGP or ictal discharges) in both the postoperative and postnatal periods in the prediction of brain injury. A *P* value <.05 was considered statistically significant.

Table I. Baseline characteristics of the study population (n = 78)

Characteristics	Values
Male sex, n (%)	59 (76)
Postnatal diagnosis, n (%)	24 (31)
Gestational age, wk, mean ± SD	39.1 ± 1.2
Birth weight, g, mean ± SD	3314 ± 506
Birth weight *z*-score, mean ± SD	−0.25 ± 0.95
CHD category, n (%)	
BVP	18 (23)
BVP-AO	32 (41)
SVP	28 (36)
5-min Apgar score, mean ± SD	9 ± 1
Neonatal death, preoperative, n (%)	2 (3)
Neonatal death, postoperative, n (%)	3 (4)
Preoperative MRI (n = 66)	
Age at scan, d, mean ± SD	8 ± 6
Brain injury, n (%)	26 (40)
WMI, moderate-severe, n (%)	21 (32)
Stroke, n (%)	8 (12)
Intraparenchymal hemorrhage, n (%)	1 (2)
Cerebral sinovenous thrombosis, n (%)	2 (3)
Postoperative MRI (n = 73)	
Postoperative age at scan, d, mean ± SD	8 ± 4
New brain injury, n (%)	43 (59)
New WMI, moderate-severe, n (%)	32 (44)
New stroke, n (%)	14 (19)
New intraparenchymal hemorrhage, n (%)	2 (3)
New cerebral sinovenous thrombosis, n (%)	15 (21)

Results

Seventy-six (near-)term neonates with critical CHD had perioperative aEEG recordings. Twenty-nine neonates also had postnatal aEEG recordings, 2 of whom died before surgery and thus did not have perioperative recordings. Baseline characteristics are presented in **Table I**. No differences in baseline characteristics were seen between the first and second cohorts (except for the CHD subgroup, as explained in Methods).

Perioperative BGPs are shown in **Figure 1**. Preoperatively (the night before surgery), the mean SAT rate was 8 ± 1 per minute, mean ISI was 5 ± 8 seconds/minute, and mean time <5 μV was 3 ± 12%. During CPB, the SAT rate was decreased (mean, 0 ± 1; $P < .001$), with increased ISI ($P = .01$) and increased time <5 μV (mean, 81 ± 28%; $P < .001$) compared with the preoperative period; no left-right differences were seen. At 48 hours after surgery, the SAT rate was still decreased compared with the preoperative rate (mean, 7 ± 3; $P < .001$), with increased ISI (mean, 10 ± 13; $P = .03$). Time <5 μV at 48 hours after surgery was comparable with the preoperative value (mean, 6 ± 16%; $P = .30$).

Abnormal postoperative BGP was seen in 18 neonates (24%; 95% CI, 14%-33%) (**Table II**). Postoperative ictal discharges were seen in 13 neonates (17%; 95% CI, 8%-26%); 4 had a single seizure (at a median of 39 hours after surgery; range, 1-68 hours), 5 had repetitive seizures (first seizure at a median of 26 hours; range, 6-43 hours), and 4 developed status epilepticus (first seizure at a median of 29 hours; range, 5-59 hours). None of the 13 neonates with ictal discharges exhibited clinical convulsions. Twelve were receiving continuous midazolam for sedation at the time of the first ictal discharge. Deterioration to abnormal BGP was more common in neonates with ictal discharges (46% vs 10%; $P = .004$). No differences were seen among CHD subgroups. The dosages of morphine and midazolam were not associated with BGP at any postoperative time point, or with abnormal BGP or with ictal discharges. In multivariable logistic regression analysis, abnormal postoperative BGP within 48 hours after surgery was independently associated with a longer duration of CPB (per 10 minutes; OR, 1.2; 95% CI, 1.0-1.3; $P = .04$). Postoperative ictal discharges were associated with repeat thoracotomy (OR, 11.0; 95% CI, 1.9-63.2; $P = .01$). The factors independently associated with lack of reaching CNV <24 hours were repeat thoracotomy (OR, 7.2; 95% CI, 1.1-47.4; $P = .04$) and culture-proven infection (OR, 12.2; 95% CI, 1.2-128.6; $P = .04$).

Postoperative MRI was available in 73 of the 76 neonates with postoperative aEEG recordings. Three neonates died during the postoperative period (all >72 hours after surgery), 1 of whom had abnormal BGP and ictal discharges in the first 48 hours after surgery. On the postoperative MRI, 43 neonates had a new brain injury (59%; 95% CI, 47%-71%). **Figure 2** displays postoperative BGPs by presence of new brain injury. As shown in **Table II**, abnormal BGP was more common in neonates with new postoperative brain injury than in those without brain injury (30% vs 13%; $P = .08$), especially when seen after the first 12 hours after surgery (23% vs 3%; $P = .02$). Ten of 11 neonates with an abnormal BGP after the first 12 hours and postoperative MRI exhibited new brain injury (OR, 8.8; 95% CI, 1.5-72.9; $P = .04$). Twelve neonates with postoperative ictal discharges underwent postoperative MRI, 11 of whom had a new brain injury (OR, 9.9; 95% CI, 1.2-82.1;

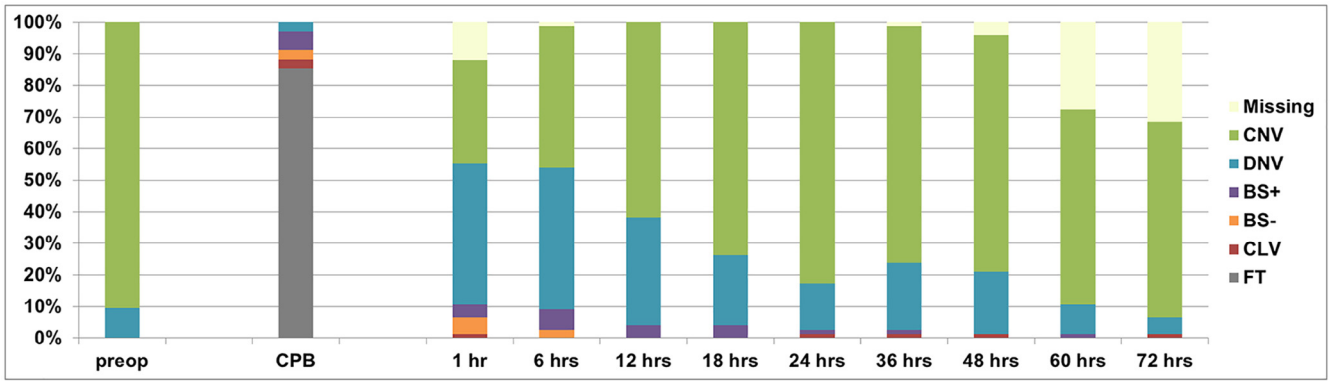

Figure 1. Preoperative, intraoperative, and postoperative BGPs at specific time points. The main reason for discontinuation of aEEG registration after 48 hours was the presence of continuous normal voltage.

$P = .03$). Abnormal brain activity (ie, abnormal BGP or ictal discharges; n = 25) was the sole risk factor associated with new postoperative brain injury (n = 43) in multivariable logistic regression analysis (OR, 4.0; 95% CI, 1.3-12.3; $P = .02$). This results in a positive predictive value of 79% (95% CI, 61%-90%) and a negative predictive value of 51% (95% CI, 43%-59%), because 25 of 51 neonates without abnormal postoperative brain activity did not have new postoperative brain injury. No significant differences were seen in SAT rate, ISI, or time <5 μV between neonates with and without new brain injury.

Postnatal aEEG was available in a subgroup of 29 neonates, 86% of which reached CNV within the first 24 hours (**Figure 3**; available at www.jpeds.com), whereas only 34% reached normal SWC within 24 hours. Seven neonates (24%; 95% CI, 8%-41%) had an abnormal BGP in the first 48 hours after birth; 1 neonate also had ictal discharges. Six of 7 neonates with an abnormal BGP required morphine (6 out of 11 with morphine had an abnormal BGP; $P = .01$). Midazolam administration was not associated with abnormal BGP ($P = .24$). Balloon atrioseptostomy was performed in 14 neonates (18%), and was the main reason for requiring postnatal morphine and/or midazolam. Preoperative MRI was available in 21 neonates. All neonates with abnormal brain activity (ie, abnormal BGP or ictal discharges; n = 7) had preoperative brain injury (n = 3) or died in the neonatal period (n = 4). None of the neonates without brain injury had an abnormal BGP. This resulted in a positive predictive value of 100% (95% CI, n/a) and a negative predictive value of 74% (95% CI, 59%-85%) for abnormal postnatal brain activity.

Gestational age was negatively associated with time <5 μV ($P = .01$). Both morphine and midazolam administration were negatively associated with SAT rate ($P < .03$), positively associated with ISI ($P < .02$), and negatively associated with time <5 μV ($P < .02$). Neonates with preoperative brain injury had decreased postnatal SAT rate (mean, 7.6/minute vs

Table II. Postoperative aEEG characteristics of the total population, neonates without new postoperative brain injury, and neonates with new postoperative brain injury

Characteristics	Total cohort	No new brain injury	New brain injury	*P* value
Preoperative	n = 63	n = 26	n = 35	
DNV, n (%)	6 (10)	1 (4)	5 (14)	.18
Normal SWC, n (%)	30 (48)	14 (54)	16 (46)	.48
Intraoperative	n = 70	n = 29	n = 38	
FT at lowest temperature, n (%)	58 (83)	22 (76)	33 (87)	.20
Duration of FT, mean ± SD	102 ± 58	87 ± 66	110 ± 53	.16
Postoperative	n = 76	n = 30	n = 43	
CNV <24 h, n (%)	67 (88)	26 (87)	39 (91)	.43
Imminent SWC <48 h, n (%)	69 (91)	26 (87)	39 (91)	.52
Normal SWC <48 h, n (%)	22 (29)	9 (30)	13 (30)	.57
Abnormal BGP, 0-48 h after surgery, n (%)	18 (24)	4 (13)	13 (30)	.08
Abnormal BGP, 12-48 h after surgery, n (%)	12 (16)	1 (3)	10 (23)	**.02**
Deterioration to abnormal BGP, n (%)	12 (16)	2 (7)	9 (21)	.08
Ictal discharges, n (%)	13 (17)	1 (3)	11 (26)	**.01**

P values for the comparison of aEEG measures between neonates with and without brain injury are presented (significant tests are shown in bold type).

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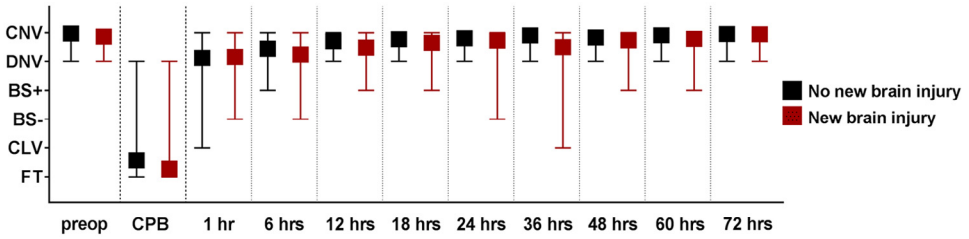

Figure 2. Preoperative, intraoperative, and postoperative BGPs at specific time points for neonates with (red) and without (black) new postoperative brain injury. Boxplots represent mean with range.

8.8/minute; $P = .03$) and increased time <5 μV (6% vs 2%; $P = .04$) when compared with neonates without preoperative brain injury.

Discussion

Our study demonstrates that abnormal brain activity (ie, abnormal BGP or ictal discharges) in the postoperative period is predictive of new brain injury in neonates with critical CHD undergoing cardiac surgery with the use of CPB. We showed that in one subgroup, abnormal brain activity in the early postnatal period is also associated with preoperative brain injury. The results of this study show that aEEG can contribute to earlier identification of neonates at the greatest risk for developing brain injury. Quantitative EEG measures (ie, SAT rate, ISI, and time <5 μV) were not predictive of brain injury in either the perioperative period or the postnatal period.

Our study shows that not only ictal discharges, but also abnormal BGP, should be considered as a clear sign of underlying brain pathology. There are 2 possible explanations for the relationship between abnormal BGP and brain injury. First, as with ictal discharges, an abnormal BGP might show the acute response of brain activity to brain injury. Second, an abnormal BGP also might be a sign of underlying (overall) brain immaturity and vulnerability (ie, brain activity is more easily depressed in response to drugs and events, and the brain requires more time to recover to normal brain activity), with the more immature brain also being at increased risk for developing brain injury.[4] This hypothesis is supported by the study of Mulkey et al showing early postnatal abnormal BGP (DNV and worse) to be related to brain atrophy.[15] In contrast to our study, however, Mulkey et al did not find a relationship between early postnatal abnormal BGP and brain injury, which might be due to defining DNV as an abnormal BGP.

Postoperative ictal discharges were seen in 17% of the neonates, which is in agreement with previous studies reporting prevalence of 11%-30%.[8,16,17] Ictal discharges were associated with new postoperative brain injury, confirming previous studies in the CHD population.[16,18] It is possible that 2-channel aEEG underestimates the prevalence of ictal discharges, because ictal discharges might arise from other brain regions besides the central region; however, it is likely that neonates with ictal discharges in other brain regions will still show an abnormal BGP.

Sedatives have been suggested to affect neonatal brain activity,[11,12] and in the CHD population especially, a (transient) effect of midazolam on the onset of SWC has been reported.[19] The more immature the brain, the more easily it is depressed by administration of sedatives.[20] In our study, the requirement for morphine in the postnatal period was related to an abnormal BGP. This was the sole factor associated with postnatal aEEG variance, which also has been reported in another study.[21] However, the administration of postnatal sedatives was related to the need for balloon atrioseptostomy. The possibility that both sedatives and hemodynamic instability could be causes of depressed brain activity should be considered.

After surgery, all neonates received morphine and midazolam, but higher dosages of morphine and midazolam were not related to abnormal brain activity. Even with morphine and midazolam, 88% of the neonates were still able to reach CNV within 24 hours after surgery. Our results suggest that even when receiving sedation, the term brain should be able to maintain a normal BGP, and that abnormal BGP, regardless of sedation, is suggestive of underlying brain pathology.

The results of our study contribute to the ongoing search for the most critical time point of brain alterations in neonates undergoing cardiac surgery. Two previous studies found a predictive value of abnormal BGP for long-term neurologic outcome when observed around 48 hours after surgery,[7,8] and both studies suggested 48 hours as a critical time point. The results of our study are in agreement with this idea, showing that an abnormal BGP obtained >12 hours after surgery is more predictive of new brain injury than an abnormal BGP obtained before this time point. At 72 hours after surgery, none of the neonates with new brain injury who were still being monitored with aEEG showed an abnormal BGP. Our study supports the hypothesis that the second and third days after surgery might be critical for optimal brain development.

SATs are normal endogenous brain activity important for normal brain development, as has been shown in the preterm population in several studies.[14,22] The SAT rate decreases when approaching term, but SATs remain detectable until at least 44 weeks postmenstrual age.[13,23] SATs should be distinguished from bursts in burst suppression, because the latter is a sign of abnormal brain activity. Current methods used for SAT detection and ISI analysis have been validated in the preterm population (with discontinuous BGP)[24] but might be less accurate in term neonates, who demonstrate continuous aEEG

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activity while awake. Although all the neonates in our study still had SATs in the postnatal and perioperative periods, the SAT rate and ISI could not differentiate between neonates with and without new brain injury. A recent study investigating SATs and ISI in neonates undergoing surgery for noncardiac congenital anomalies also failed to find a relationship between quantitative EEG measures and postoperative brain injury.[13] In our study, qualitative aEEG characteristics, such as BGP and ictal discharge, seem to be more important in the identification of (term) neonates at the greatest risk for developing brain injury, especially in the postoperative period, and are easier to examine at the bedside.

Our study could not identify lack of recovery to CNV or SWC as a marker of new postoperative brain injury. Several previous studies have reported an association between lack of recovery to CNV or SWC within 48 hours after surgery and worse motor outcomes in children with CHD.[7,8] However, the majority of our cohort reached CNV within 24 hours after surgery, and only 2 of the 76 neonates did not reach CNV within 48 hours after surgery. Although it was identified as a risk factor for impaired neurodevelopment in a previous study,[25] the duration of FT during CPB was not associated with new brain injury in our cohort of neonates with CHD.

Our study highlights the importance of continuous bedside neuromonitoring before and after cardiac surgery in neonates with CHD. The results of this study are generalizable, although differences in aEEG and MRI protocols can cause variability in abnormal aEEG brain activity and MRI brain injury prevalence. An increasingly popular intervention is the use of neuroprotective agents for prevention and regeneration of brain injury in this population. aEEG might be useful in the implementation and application of such interventional strategies given its apparent ability to identify neonates at the greatest risk for brain injury at an early stage.

Our study has several limitations. First, we used 2-channel aEEG, which might underestimate the prevalence of ictal discharges. However, as described previously, it is likely that neonates with ictal discharges in other brain regions besides those monitored with aEEG still show an abnormal BGP. Second, current detection methods for SAT and ISI are validated in the preterm population and thus are most reliable when discontinuous aEEG activity is present. Term neonates show discontinuous activity during quiet sleep; however, quiet sleep could not be taken as a criterion for epoch selection in our population, because most neonates did not exhibit SWC during the aEEG-recorded periods. Third, the study population was scanned using 2 different MRI systems (1.5 and 3 T); however, no difference was seen in brain injury incidence between the 2 MRI systems. Finally, only a small number of neonates had postnatal aEEG recordings, which limited the statistical power for the relationship between postnatal aEEG and preoperative brain injury. Moreover, neonates with a postnatal diagnosis were often admitted after 48 hours of life, limiting the possibility of investigating this important risk factor.

This study shows that postoperative abnormal aEEG-measured brain activity is an early, bedside marker of new brain injury in neonates undergoing cardiac surgery for critical CHD, with abnormal BGP and ictal discharges being clear signs of underlying brain pathology. Qualitative aEEG characteristics seem to be more predictive of brain injury than quantitative aEEG and EEG measures. ■

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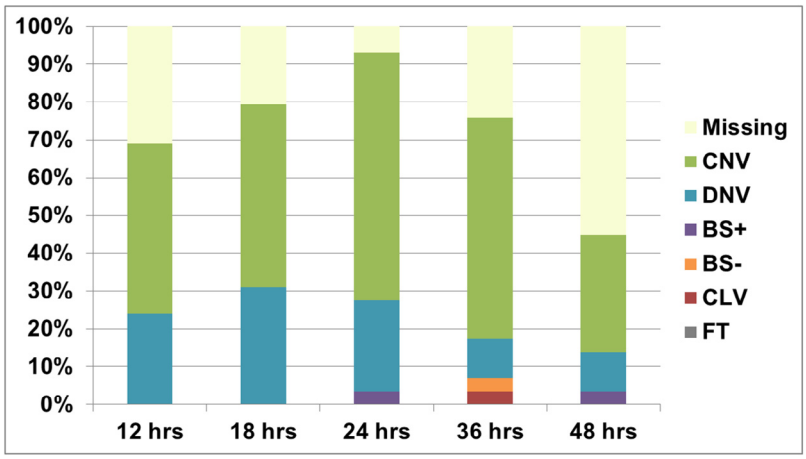

Figure 3. Postnatal BGPs at specific time points. The main reason for discontinuation of aEEG registration after 24 hours was the presence of continuous normal voltage.

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