



October 2008: VOLUME 6, NUMBER 2

Special Announcement



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The Amplitude-Integrated EEG (aEEG) and Neonatal Intensive Care

In this Issue...

Alterations in the neurologic status of neonates may be challenging to detect because of their often-subtle nature and the relatively infrequent need to conduct detailed neurologic assessments. Use of the amplitude-integrated electroencephalogram (aEEG) is increasingly being advocated to facilitate assessment of brain activity in sick neonates and to supplement and/or guide the utilization of conventional EEG. The overall role of aEEG as a monitoring device in neonatal intensive care units is evolving, with changes in the technology used for display and analysis of the acquired data.

In this issue, we examine the aEEG in order to understand its relationship to information derived from conventional EEG tracings (background activity and seizure detection), its utility in predicting neurodevelopmental outcome in infants with neonatal encephalopathy, and its use as a marker for following neurologic maturation of the brain of premature infants.



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Guest Faculty Disclosure

Dr. Laptook has no relevant financial relationships to disclose.

Dr. Sommers has no relevant financial relationships to disclose.

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At the conclusion of this activity, participants should be able to:

- Describe to colleagues the relationship between recordings acquired using amplitude-integrated EEG (aEEG) and conventional EEG
- Discuss with colleagues the ability of aEEG to detect seizure activity
- Explain to colleagues the strengths and weaknesses of aEEG results when applied to predict outcome following hypoxia-ischemia, and to serially assess brain maturation

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In this audio interview Dr. Laptok discusses where aEEGs have been most beneficial, the current research as relates to very pre-term and late-preterm infants, and the potential clinical applications of the aEEG.

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COMMENTARY

The amplitude-integrated electroencephalogram (aEEG) is a bedside device used for assessing cerebral electrical activity. The aEEG recording represents a signal from an EEG channel that is transformed using signal amplification, passage through an asymmetric bandpass filter to attenuate signals $< 2\text{Hz}$ and $> 15\text{Hz}$, semilogarithmic amplitude compression, rectification, and time compression. The original aEEG used a single cross-cerebral channel displayed on a semilogarithmic scale at a speed of 6 cm per hour, along with impedance.¹ The result was a band of activity that could be characterized by the upper and lower voltage borders, leading to a description of patterns that non-electroencephalographers could recognize without any formal EEG training. Currently, the role of aEEG in neonatal intensive care units (NICUs) remains unclear; the spectrum ranges from a frequently used device that complements formal EEG for surveillance and monitoring of potential CNS abnormalities to consideration of aEEG as a research tool.

The areas of research most extensively investigated using aEEG include assessment of background activity in newborn encephalopathy and seizure detection. As the 1999 al Naqeeb and Toet articles (reviewed in this issue) discuss, aEEG performed shortly after birth in infants with a diagnosis of perinatal asphyxia or encephalopathy has an encouraging predictive profile for adverse outcomes of death or cerebral palsy assessed beyond 1 year of age. These results are consistent with others reviewed in a recent meta-analysis.² The aEEG was used as the final step for inclusion criteria (after fulfilling clinical, biochemical, and neurologic assessments) in the Cool-Cap Trial, which evaluated therapeutic hypothermia for neonatal encephalopathy;³ the rationale for using aEEG was to improve the specificity of case selection. At 18 months of age, the rate of death or severe disability among noncooled, control infants in Cool-Cap was 66%. What remains puzzling is that in the National Institute of Child Health and Human Development (NICHD) Whole-Body Hypothermia Trial, which had similar inclusion criteria but did not use an aEEG, the rate of death or severe/moderate disability at 18 to 22 months of age was 62% in noncooled, control infants.⁴ Moderate disability occurred in only 1 control infant in the NICHD trial, which minimizes the differences in disability criteria between the 2 trials. These observations are difficult to reconcile with the published predictive value of aEEG, in addition to a high level of agreement for pattern classification among multiple observers. Considerations that may affect the use of aEEG include: 1) the expertise of individuals interpreting the aEEG under study and clinical conditions; 2) subjective assessments to assign a pattern, particularly if voltage straddles a cutoff value; 3) limitations of the aEEG in detecting seizures; and 4) use of short recording intervals (eg, 30 minutes) to accurately reflect cerebral activity. Artifacts on aEEG recordings have been noted (up to 12% of recording time) and may be secondary to electrical interference or muscle activity.⁵ Some investigators have questioned using aEEG as an inclusion criterion for therapeutic

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hypothermia, based on poor negative predictive value for short-term outcomes.⁶

Interest in the use of aEEG for detection of seizures is high among clinicians, given the diverse phenotypes of neonatal seizures, possible clinical-electrographic dissociation, and limitations in obtaining a conventional EEG on short notice in many centers. Based on the positioning of the electrodes, it is well recognized that seizures remote from the recording electrodes will not be detected. Some newer aEEG devices provide interhemispheric channels, in addition to the traditional cross-cerebral channels. Time compression facilitates inspection and monitoring of background activity, but limits detection of short seizures. Identification of electrographic seizures using aEEG has improved with the availability of the raw EEG on newer aEEG devices. As discussed in the Shah and Shellhaas articles, reviewed in this issue, availability of the raw EEG and the expertise of individuals interpreting the recording affect seizure detection, thus raising the issue of whether nonelectroencephalographers can receive sufficient training to use aEEG as an adjunct to conventional EEG for seizure detection.

The aEEG is an attractive device since it provides potential information not readily available in most NICUs. Use of the aEEG has been improved with respect to proper electrode application and attainment of desired impedance, to facilitate implementation by providers without a background in EEG. Other areas currently being investigated will ultimately determine overall use of aEEG in the NICU. Characterization of background activity in a nonbiased, objective manner is essential; incorporation of software to analyze aEEG tracings may improve the value of aEEG in predicting neurodevelopmental outcome. The aEEG will probably be better suited as a screening tool for seizure detection when validated computerized seizure detection algorithms are incorporated into the software. Although the clinical importance of electrographic seizures remains uncertain, determination of whether abnormal movements/behaviors are seizure equivalents is an important issue for clinicians to research.

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4. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, et al; National Institute of Child Health and Human Development Neonatal Research Network. [Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy](#). *N Engl J Med*. 2005;353(15):1574-1584.
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COMPARISON OF BACKGROUND ACTIVITY USING aEEG vs SIMULTANEOUS CONVENTIONAL EEG IN FULL-TERM NEONATES

Toet MC, van der Meij W, de Vries LS, Uiterwaal CS, van Huffelen KC. **Comparison between simultaneously recorded amplitude integrated electroencephalogram (cerebral function monitor) and standard electroencephalogram in neonates.** *Pediatrics*. 2002;109(5):772-779.

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Since single-channel amplitude-integrated electroencephalograms (aEEGs) are being used more frequently in neonatal intensive care units (NICUs), it is important to understand the relationship between the recordings on this device and those on conventional EEGs (cEEGs). Toet and colleagues evaluated the concordance of background pattern and epileptiform activity recorded with simultaneous aEEG vs cEEG in 36 late-preterm or full-term infants. This summary will focus on background activity, since 2 other reports included in this series will examine seizures detected with aEEG in more detail. More than two-thirds of the infants were diagnosed with hypoxic-ischemic encephalopathy; the remaining infants had parenchymal hemorrhage, infarction, hypoglycemia, or seizures with no etiology. The aEEG tracings were independently evaluated by 2 neonatologists with expertise in this area and were categorized into 5 background patterns, based on the authors' prior work: 1) continuous normal voltage; 2) discontinuous normal voltage; 3) burst-suppression; 4) continuous low voltage; and 5) flat tracing. The cEEG tracings were evaluated by 2 experienced clinical neurophysiologists and categorized into 6 background patterns, based on published literature: 1) normal; 2) depressed; 3) excessive discontinuity; 4) burst-suppression; 5) low voltage undifferentiated; and (6) no activity.

Three EEG tracings could not be interpreted due to artifact. A continuous normal voltage background on aEEG (n=10) corresponded to a normal or depressed EEG background in all but 1 that had excessive discontinuity. A discontinuous normal voltage background on aEEG (n=10) corresponded to a depressed or excessively discontinuous EEG background. A burst-suppression background on aEEG (n=8) corresponded to excessive discontinuity or a burst-suppression on EEG background. A flat tracing or continuous low voltage (n=5) on aEEG corresponded to an undifferentiated or absent background activity on EEG background. A severely abnormal aEEG tracing (defined as burst-suppression, continuous low voltage, and flat tracing) was able to predict a severely abnormal EEG tracing (excessive discontinuity, burst-suppression, low voltage undifferentiated, no activity) with a sensitivity of 72%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 75%. A normal aEEG tracing (continuous or discontinuous normal voltage) had a sensitivity of 75% for a normal EEG pattern (normal, depressed). Inter-observer agreement on background activity of the aEEG was achieved in 31 of 33 cases ($\kappa=0.92$), compared with agreement on background activity using the EEG in 27 of 33 cases ($\kappa=0.74$).

The authors concluded that the aEEG appears to be a valid device for monitoring electroencephalographic background activity. They cautiously recommend using intermittent standard EEG recordings whenever there is any difficulty classifying background activity.

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DETECTION OF ELECTROGRAPHIC SEIZURES USING aEEG AND CONVENTIONAL ELECTROENCEPHALOGRAPHY

Shellhaas RA, Soaita AI, Clancy RR. **Sensitivity of amplitude-integrated electroencephalography for neonatal seizure detection.** *Pediatrics.* 2007;120(4):770-777.

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Shah DK, Mackay MT, Lavery S, et al. **Accuracy of bedside electroencephalographic monitoring in comparison with simultaneous continuous conventional electroencephalography for seizure detection in term infants.** *Pediatrics.* 2008;121(6):1146-1154.

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Shellhaas and associates retrospectively compared seizure activity determined by conventional electroencephalograms (cEEGs) vs amplitude-integrated electroencephalograms (aEEGs). In this study, a convenience sample of cEEG tracings was used that was known to contain electrographic seizures. A total of 125 cEEGs were obtained from 121 infants with a postconceptional age of 34 to 50 weeks and provided 851 seizures, as interpreted by 2 experienced pediatric electroencephalographers. An additional 19 cEEGs were added that did not contain electrographic seizures. The aEEG was constructed digitally by using a single channel of each cEEG (C3-C4), and was interpreted by 6 neonatologists with varying experience in aEEG by marking the initiation and termination of seizure activity. The neonatologists did not have access to the raw EEG from the C3-C4 channel of the cEEG. Of the 125 cEEG recordings, 118 (94%) had seizure activity in the C3-C4 lead. Of the 125 recordings with seizures, at least 1 seizure episode was detected by the neonatologists in 40% \pm 17% (range, 22% to 57%) of the recordings, with a detection rate of 26% \pm 11% (12% to 38%) of all seizure episodes. At least 1 seizure episode was detected by all neonatologists in 19 of 125 recordings (15%), and only 1 of the recordings had all seizures detected by all of the neonatologists. Among 19 recordings without seizures, no false-positive seizures were recorded by any of the neonatologists. Thus, the sensitivity of aEEG for detecting seizures is low but the specificity is high. Multivariate analysis indicated that the following variables were associated with detection of seizures by aEEG: 1) seizure present on the single channel of C3-C4; 2) neonatologists' level of aEEG expertise; 3) frequency of seizures; 4) seizure amplitude; and 5) and seizure duration. Based on these results, the authors concluded that the aEEG has important limitations in the diagnosis and quantification of neonatal seizures.

In a smaller data set (21 infants, 7 of whom had seizures), Shah and coworkers compared detection of electrographic seizures using aEEG vs cEEG. Comparisons were performed among 1) cEEG interpreted independently by experienced neurologists; 2) aEEG using 2 channels (C3-P3 and C4-P4) and their respective raw EEG tracings by 2 experienced aEEG users; and 3) aEEG using interhemispheric and cross-cerebral channels (C3-P3, C4-P4, and P3-P4) without the raw EEG tracings by 2 experienced aEEG users. The 7 infants with seizures were full-term and had a spectrum of underlying diagnoses as etiologies for the seizure. Based on the cEEG, 41 non-status epilepticus seizures were detected. Use of the aEEG with the raw EEG tracings led to a 76% sensitivity, a 78% specificity, a 78% positive predictive value, and a 78% negative predictive value for detection of seizures compared with cEEG. In contrast, use of the aEEG without the raw EEG tracings led to a sensitivity of 56% with a single cross-cerebral channel and a sensitivity of 44% using 2 interhemispheric channels for detection of seizures. False-positive results for seizures detected by aEEG occurred with or without access to the raw EEG tracings and were attributed to muscle or cup electrode artifacts. The kappa values for the level of agreement among each pair of individuals interpreting the EEG data were 0.84 (high level of agreement) with the cEEG, 0.67 (substantial level of agreement) with the aEEG with access to the raw EEG tracings, and 0.31 (fair agreement) with the aEEG alone.



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These results support the notion that use of an aEEG in combination with raw EEG tracings is superior to use of an aEEG alone for seizure detection, with better agreement among independent interpreters. The authors concluded that skilled providers are able to use an aEEG along with the raw EEG tracings to provide acceptable sensitivity, specificity, and predictive values for seizure detection.

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PREDICTION OF EARLY CHILDHOOD NEURODEVELOPMENTAL OUTCOME USING aEEG FOLLOWING NEONATAL ENCEPHALOPATHY

Toet MC, Hellström-Westas L, Groenendaal F, Eken P, de Vries LS. **Amplitude integrated EEG 3 and 6 hours after birth in full term neonates with hypoxic-ischaemic encephalopathy.** *Arch Dis Child Fetal Neonatal Ed.* 1999;81(1):F19-F23.

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al Naqeeb N, Edwards AD, Cowan FM, Azzopardi D. **Assessment of neonatal encephalopathy by amplitude-integrated electroencephalography.** *Pediatrics.* 1999;103(6 pt 1):1263-1271.

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Toet and colleagues evaluated amplitude-integrated electroencephalograms (aEEGs) performed at 3 or 6 hours following birth to predict adverse outcomes in term infants with a diagnosis of perinatal asphyxia (based on fetal decelerations, acidemia, delayed onset of respirations at birth, and end-organ dysfunction). A total of 68 infants were studied at 2 centers over a 10-year period and were followed during early childhood. An adverse outcome was defined as death, cerebral palsy, or a global developmental delay diagnosed after 1 year of age using standardized tests. The aEEG recording was classified into 5 categories using pattern recognition as follows: 1) a flat tracing; 2) continuous extremely low voltage; 3) burst-suppression; 4) discontinuous normal voltage; and 5) continuous normal voltage. The first 3 patterns were considered abnormal. The sensitivity and specificity of an abnormal aEEG pattern for predicting an adverse outcome at 3 hours were 85% and 77%, respectively, with positive and negative predictive values of 78% and 84%, respectively. These results were modestly improved using the 6-hour aEEG, with a sensitivity and specificity of 91% and 86%, respectively, and positive and negative predictive values of 86% and 91%, respectively. A change in aEEG pattern between 3 and 6 hours was reported in 31% (21 of 68) of the infants; improvement in aEEG was reported in 7 and deterioration was reported in 14 of the infants. The change in aEEG led to a change from a normal to an abnormal category of aEEG in only 2 of the infants with deterioration. The authors concluded that use of an aEEG 3 hours after birth can accurately predict early childhood neurodevelopmental outcome among infants with a diagnosis of perinatal asphyxia.

al Naqeeb and associates also evaluated the predictive value of aEEG in 56 late- preterm and full-term infants with acute encephalopathy of varying etiologies (40 were suspected to be hypoxic-ischemic in origin). Recordings of aEEG were acquired between 2 hours and 21 days. Analyses were performed in all infants, including those with hypoxic-ischemic encephalopathy (HIE) and those with an aEEG performed at <12 hours (median, 5 hours). Neurodevelopmental outcome was assessed at 18 to 24 months using the Griffith's General Quotients. In addition, 14 healthy, full-term infants were studied at <12 hours after birth and were used to define a classification system based on voltage criteria. Normal amplitude was defined as an upper and lower margin of aEEG activity >10 μ V and >5 μ V, respectively. Moderately abnormal amplitude was defined as an upper and lower margin of aEEG activity >10 μ V and \leq 5 μ V, respectively. A suppressed amplitude was defined as an upper and lower margin of aEEG activity <10 μ V and <5 μ V, respectively, usually accompanied by a burst of high-voltage activity. Any of these groups could be accompanied by a seizure pattern (sudden increase in amplitude and narrowing of the aEEG band). Of 21 infants with a normal aEEG, 19 were normal at follow-up; of 35 infants with an abnormal aEEG, 27 were abnormal at follow-up. Predictive values for an abnormal

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outcome using aEEG were a sensitivity of 93%, a specificity of 70%, and positive and negative predictive values of 77% and 90%, respectively. Predictive values for infants with HIE were modestly improved. In the 24 infants studied within 12 hours of birth, the sensitivity was 100%, the specificity was 82%, and the positive and negative predictive values were 85% and 100%, respectively. The authors concluded that aEEG provides a high predictive value for neurodevelopmental outcome in infants with acute encephalopathy, including those with HIE.

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POSTNATAL BRAIN MATURATION IN PREMATURE INFANTS EVALUATED BY aEEG

Burdjalov VF, Baumgart S, Spitzer AR. **Cerebral function monitoring: a new scoring system for the evaluation of brain maturation in neonates.** *Pediatrics.* 2003;112(4):855-861.

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Early publications with amplitude-integrated electroencephalograms (aEEGs) have categorized recordings based on pattern recognition using descriptive or semiquantitative criteria. Burdjalov and coworkers addressed the classification of aEEG recordings by developing a scoring method based on 4 components of the aEEG and applying it to categorize maturational changes of premature infants. The components of their scoring system included 1) presence or absence of sleep-wake cycles, defined as intermittent widening of the aEEG leading to greater maximum and minimum voltage amplitudes; 2) amplitude of the lower border, assessed by best fit of a line visually drawn through the lower border; 3) the bandwidth, representing the voltage span from peak signal to trough; and 4) presence of continuity, indicated by tightly compressed recordings due to frequent alternating electrical activity. Low levels of continuity, also termed discontinuous, were characterized by a reduced number of electrical variations with a less compressed tracing.

Scoring was applied to 30 infants with gestational ages from 24 to 39 weeks (median, 27 weeks, with only 1 infant older than 34 weeks) who were without brain pathology (intraventricular hemorrhage, periventricular leukomalacia, or hypoxic-ischemic encephalopathy) or sedative medication. Serial aEEGs were recorded at <3 days, and then weekly or biweekly until discharge. These yielded 146 recordings (median, 4.5 recordings per infant) and data plots extending from 26 to 34 weeks postconception. The aEEGs of infants with extreme prematurity (gestational age <26 weeks) were predominantly discontinuous, with rudimentary or absent sleep-wake cycles, depressed lower border amplitude, and a broad bandwidth. Sleep-wake cycling emerged after 27 weeks and was more recognizable after 29 weeks. Continuity increased progressively, attaining its maximum score by 30 to 31 weeks. The lower border amplitude increased after 27 weeks and reached its peak between 29 and 34 weeks. The bandwidth score increased over the postconceptual age-range studied. The correlation coefficient between the composite score and postconceptional age was 0.84. Correlation coefficients between individual components of the aEEG and postconceptional age ranged from a high value of 0.83 for sleep-wake cycles to a low value of 0.46 for the lower border amplitude.

The authors concluded that although the scoring system has inherent subjectivity within the component variables, it could serve as a template for additional nonbiased assessments of aEEG using digitized recordings and computerized analyses.

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- Describe to colleagues the relationship between recordings acquired using amplitude integrated EEG (aEEG) and conventional EEG
- Discuss with colleagues the ability of aEEG to detect seizure activity
- Explain to colleagues the strengths and weaknesses of aEEG results when applied to predict outcome following hypoxia-ischemia, and to serially assess brain maturation

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- **Edward E. Lawson, MD** has indicated a financial relationship of grant/research support from the National Institute of Health (NIH). He also receives financial/material support from Nature Publishing Group as the Editor of the *Journal of Perinatology*.
- **Christoph U. Lehmann, MD** has received grant support from the Agency for Healthcare Research and Quality and the Thomas Wilson Sanitarium of Children of Baltimore City.
- **Lawrence M. Nogee, MD** has received grant support from the NIH.
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