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REVIEW

Using amplitude-integrated EEG in neonatal intensive care

JD Tao and AM Mathur

Department of Pediatrics, Washington University School of Medicine, St Louis, MO, USA

The implementation of amplitude-integrated electroencephalography (aEEG) has enhanced the neurological monitoring of critically ill infants. Limited channel leads are applied to the patient and data are displayed in a semilogarithmic, time-compressed scale. Several classifications are currently in use to describe patient tracings, incorporating voltage criteria, pattern recognition, cyclicity, and the presence or absence of seizures. In term neonates, aEEG has been used to determine the prognosis and treatment for those affected by hypoxic–ischemic encephalopathy, seizures, meningitis and even congenital heart disease. Its application as inclusion criteria for therapeutic hypothermia remains controversial. In preterm infants, normative values and patterns corresponding to gestational age are being established. As these standards emerge, the predictive value of aEEG increases, especially in the setting of preterm brain injury and intraventricular hemorrhage. The sensitivity and specificity of aEEG are enhanced by the display of a simultaneous raw EEG, which aids interpretation. Caution must be taken when using and interpreting this tool in conjunction with certain medications and in the setting of less experienced staff. Continuing efforts at developing software that can aid seizure detection and background classification will enhance the bedside utility of this tool.

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Introduction

Recognizing the need for neurological monitoring in critically ill neonates, neonatologists and neurologists are becoming more familiar and comfortable with the use of amplitude-integrated electroencephalography (aEEG) in the neonatal intensive care unit (NICU). The availability of simultaneous raw EEG tracing alongside the aEEG trace has significantly enhanced the sensitivity and specificity of aEEG in the detection of background and seizure activity.[1] This established, yet novel use of continuous brain monitoring can be applied, for example, to infants admitted with encephalopathy, seizures or other brain malformations. Both term and preterm infants may benefit from the clinical application of aEEG findings. Much similar to continuous monitoring of vital signs, bedside aEEG can help guide decision-making in real time for infants admitted to the NICU. This article will review the history, classification and application of aEEG in both term and preterm infants.

Correspondence: Dr AM Mathur, Division of Newborn Medicine, St Louis Children's Hospital, One Children's Place, St Louis, MO 63110, USA.
E-mail: mathur_a@kids.wustl.edu

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Background

Starting in the 1960s, Maynard *et al*.,[2] developed the first use of an instrument to study cerebral activity in resuscitated patients with suspected brain damage. Referred to as the cerebral function monitor (CFM), its application evolved over the next two decades to include neonates, both term and preterm. By the mid-1980s, normal CFM patterns of healthy and encephalopathic term infants were described. Soon after, the technique was applied to preterm babies to monitor acute signs of cerebral change and brain injury. Data from premature infants continue to evolve, especially in terms of prognosis.[3] More recently, the establishment of aEEG as inclusion criteria for neuroprotective strategies has emerged,[4,5] and its application in newborns with both pulmonary hypertension and congenital heart disease is increasing.[6] Whatever the case, newer monitoring devices incorporating both aEEG and the raw EEG trace continue to develop and are beginning to be integrated into the routine care of the critically ill infant in the NICU.

The aEEG trace is extracted from a limited number of channels of the conventional EEG (cEEG), and is both time compressed and filtered before display. Typically, leads are placed on a single pair of biparietal locations (P3 and P4) or modified to add an additional lead on each side (C3 and C4) (Figure 1). Two studies have compared the two techniques and found the bihemispheric method to be superior, especially in infants with unilateral brain injury.[7,8] Multichannel use has shown greater sensitivity in seizure detection as well.[9] The scalp locations are adopted from the international 10 to 20 neonatal EEG sensor positions, and produce a signal that must be enhanced and displayed in a semilogarithmic scale. From 0 to 10 μV the scale is linear and from 10 to 100 μV the scale is logarithmic. In this way a signal at lower amplitude is enhanced, whereas a signal at higher amplitude is attenuated. A typical

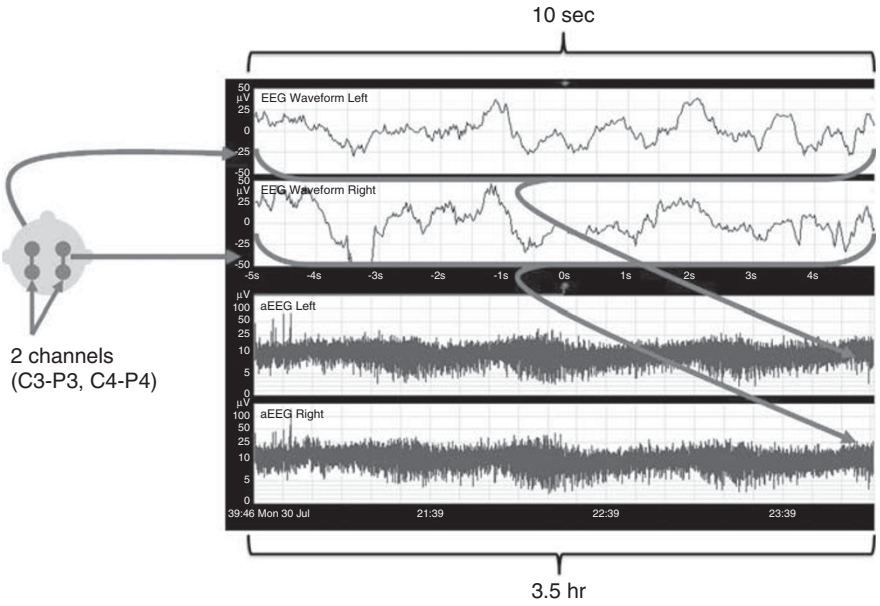

Figure 1 Two pairs of bihemispheric leads are present, corresponding to the standard electroencephalography (EEG) system. The raw EEG signal from the two channels is displayed above the time-compressed amplitude-integrated EEG (aEEG) tracing.

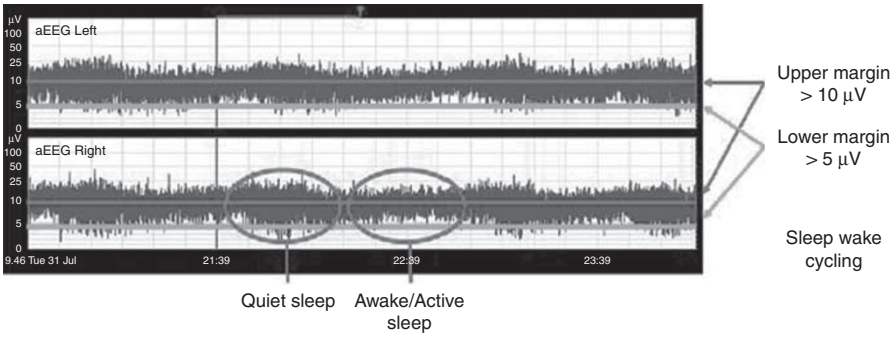

Figure 2 Note the varying bandwidth from 0 to 10 μV (linear) and from 10 to 100 μV (logarithmic) on both tracings. Sleep–wake cycling is clearly evident. aEEG, amplitude-integrated electroencephalography.

monitor displays the aEEG bandwidth, which reflects the trend of maximum and minimum amplitudes at a speed of 6 cm h^{-1}. The speed can be customized on some monitors, and the raw EEG tracing is shown simultaneously on most as well. Finally, seizure detection algorithms are being tested in some devices to assist nonexperts in quantifying seizure burden, although none of them are approved by the Food and Drug Administration at this time.[10,11]

aEEG classification

Much similar to cEEG, the basic interpretation of aEEG is primarily based on pattern recognition of background activity. Al Naqeeb *et al*.[12] used simple voltage criteria to characterize the aEEGs of normal and encephalopathic term infants. The background pattern was classified as normal (upper band >10 μV and lower band <5 μV), moderately abnormal (upper band >10 μV and lower band <5 μV) or suppressed (upper band <10 μV and lower band <5 μV) (Figure 2). Interobserver agreement was excellent for voltage amplitude and the use of this scheme accurately predicted neurodevelopmental outcome at 18 to 24 months. On the other hand, Hellström-Westas *et al*.[13] used pattern recognition as well as voltage criteria to describe aEEG patterns in term and preterm infants. This method, not unlike that used by Toet *et al*.,[14] uses cEEG terminology (for example, burst suppression, isoelectric tracing, trace alternant). The background pattern is continuous, discontinuous, burst suppression, continuous low voltage or flat/isoelectric, and specific voltage criteria are used as well (Figure 3). The purpose of such a modified proposal was to introduce a system applicable to newborns of all ages and diagnoses.

Regardless of which classification method is used, caution must be taken when interpreting and applying specific aEEG patterns. A recent multicenter study comparing the simple system by al Naqeeb *et al*.[12] versus the advanced scheme by Hellström-Westas *et al*.[13] showed that interobserver agreement was better when using

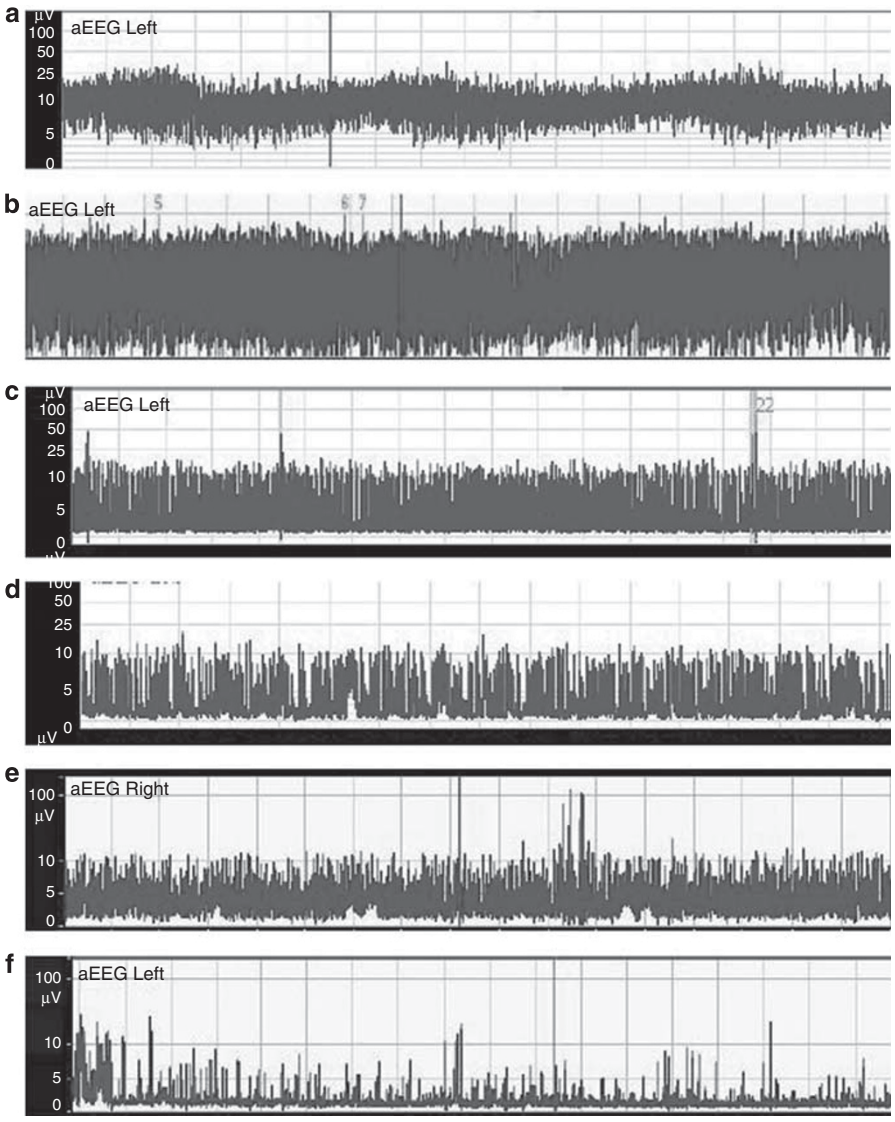

Figure 3 (**a**) Continuous background pattern, with prominent SWC: upper-margin voltage is >10 μV and lower margin voltage is >5 μV. (**b**) Discontinuous background pattern: upper margin is >10 μV and lower margin is <5 μV. (**c**, **d**) Burst suppression pattern: upper and lower margin voltages are <10 and <5 μV, respectively, with >100 bursts per hour (**c**) and <100 bursts per hour (**d**). (**e**) Continuous low voltage: upper margin is <10 μV and lower margin is <5 μV. Occasional spikes are seen over 10 μV. (**f**) Isoelectric or flat tracing: both margins are <5 μV and prominent spikes are likely due to patient movement. aEEG, amplitude-integrated electroencephalography.

the simple technique.[15] This was regardless of the level of training and the presence or absence of seizures. Notably, however, the aEEG machines used in the study did not display or contain the raw EEG data, which may help to delineate the discrepancies due to suspected artifacts. Still, when compared with cEEG, interobserver agreement was only fair for both of the techniques used.

aEEG in the term neonate

The aEEG background pattern is known to be an early predictor of brain injury in term infants with hypoxic–ischemic encephalopathy (HIE). Poor prognostic indicators include burst suppression, continuous low voltage or flat/isoelectric tracing. Low voltage (<4 μV) can also predict adverse developmental outcome.[16] Several studies have shown that 6 to 12 h of life is the time period during which the aEEG background is most valuable.[12,17,18] Sensitivities in these studies range from 91 to 100%, with positive predictive values of ~85%. A recent study showed that the combination of early aEEG and clinical examination within the first 12 h of birth increased the positive predictive value and specificity compared with either method alone.[19] The duration of monitoring may be important as well, as several studies advocate longer monitoring beyond 24 h. A retrospective study in 2004 indicated that recovery of the background pattern to normal is not uncommon, and that the sooner the background pattern normalized, the better the

prognosis.[20] Similarly, van Rooij *et al*.[21] showed that in infants with severely abnormal patterns at 6 h, recovery to normal by 24 h resulted in mild or no disability in 61% of infants.

Sleep–wake cycling (SWC) can also be used to determine prognosis in term infants with HIE, and is characterized as regular variations in aEEG bandwidth (Figure 2). Typically, a narrow bandwidth characterizes wakefulness and active sleep, whereas a wider bandwidth denotes quiet sleep.[22] In addition to normal and abnormal sleep–wake cycles, Hellström-Westas *et al*.[13] suggest that an intermediate category of imminent/immature SWC be added to the presence or absence of cycling.[13] Infants with HIE have noticeable differences in SWC with regard to severity of encephalopathy. A shorter time of onset, increased duration of active sleep and quality of SWC can all provide prognostic value in these cases.[23,24] Further studies are necessary to examine the relationship between aEEG and SWC in these scenarios, especially in infants undergoing therapeutic hypothermia.

Full-term infants with seizures also benefit from the use of aEEG. In addition to those with neonatal encephalopathy, there are multiple indications for its application, including congenital malformations, stroke, metabolic disorders, meningitis[25] and encephalitis. Although the gold standard for diagnosis and treatment may be standard video-EEG monitoring, this is not feasible or practical in the majority of neonatal units around the world. Several studies examined the utility of aEEG in comparison with conventional and/or video-EEG in this infant population, finding that aEEG was not only reliable but also complemented cEEG in more than one aspect.[14,26] A recent pilot study on the feasibility of aEEG in our tertiary-care NICU showed that 73% of seizures >30 s and 87% >60 s were detected by the aEEG seizure algorithm.[27] Furthermore, when compared with a blinded study group, patients whose tracings were visible to bedside physicians showed a trend toward reduced seizure burden without evidence of overtreatment.

The presence of the raw EEG signal on the aEEG monitor may add more value to seizure detection. In the study by Lawrence *et al*.,[27] neonatologists had access to the limited-channel unprocessed EEG signal. However, physicians without access to this raw signal may have more difficulty. Shellhaas *et al*.[28] generated aEEGs from single-channel cEEG tracings and had the data examined by neonatologists with varying levels of expertise. Without the raw signal available to them, physicians detected seizures in 22 to 57% of EEGs, and correctly identified 12 to 38% of individual seizures. Shorter duration and lower seizure amplitude on aEEG were the reasons cited for such low sensitivity. Similarly, Shah *et al*.[1] conducted a study comparing single-channel aEEG, two-channel aEEG and two-channel aEEG combined with the raw EEG signal. Interobserver agreement was high (0.67), with sensitivity and specificity approaching 80% when two-channel aEEG was used with simultaneous raw EEG. Tracings reviewed by experienced readers without the raw EEG signal showed low sensitivity (27 to 56%) and low interobserver agreement (0.29 to 0.31).

Seizures can be identified on aEEG as a rapid rise in both the lower and upper margins of the amplitude tracing (Figure 4). Along with the revised background pattern and SWC classification, Hellström-Westas *et al*.[13] categorize seizures as single, repetitive (more frequent than 30-min intervals) and status epilepticus (ongoing activity >30 min). As noted above, the importance of the raw tracing cannot be minimized, and should show simultaneous seizure activity indicated by repetitive spikes or sharp waves. With such classifications and detection techniques, the question of what one should do with this information still remains. Data do show an association between electrographic seizure burden and clinical outcome,[29] but the treatment of subclinical seizures remains unclear.[30] Clinical studies are currently being undertaken to determine whether the treatment of EEG-detected seizures improves mortality and neurodevelopmental outcome. Similarly, several studies have addressed the incidence of post-neonatal epilepsy after the onset of neonatal seizures.[31,32] Commonly cited as anywhere from 20 to 50% after treating clinical events, Toet *et al*.[32] demonstrated that only 9.4% out of a total of 204 term infants who were treated for clinical and subclinical seizures developed epilepsy.

The use of aEEG in screening for potential neuroprotective strategies such as hypothermia remains controversial. Although al Naqeeb *et al*.[12] and Shalak *et al*.[19] both advocate aEEG for assessing term infants at risk for encephalopathy, only two major trials to date have used this tool as entry criteria for hypothermia.[4,5] The Cool Cap Study[5] adopted the quantitative al Naqeeb method[12] and randomized patients with moderately or severely abnormal background voltage, seizure activity or both. The TOBY trial used the same method but required an abnormal background pattern for a 30-min duration or the presence of seizures as part of their criteria.[4] Two other major trials of hypothermia do not include aEEG in their selection criteria.[33,34] Sarkar *et al*.[35] addressed this very issue, noting a low negative predictive value of a normal or less severe aEEG in infants diagnosed with encephalopathy. This was likely related to the occurrence of electrocardiographic artifact on the aEEG leading to an elevation of the amplitude baseline. This study concluded—and instituted a change in practice reflecting such—that aEEG should not be used as a selection criterion. The data are scarce, however, on using aEEG during and/or after hypothermia for neuroprotection.[36–38] One small study examined 26 infants undergoing extracorporeal membrane oxygenation who were concomitantly cooled and monitored with aEEG. Results showed that mild hypothermia did not affect aEEG amplitude before 48 h and could add information to clinical status.[37] Yet another small cohort from Sweden underwent selective hypothermia and demonstrated that normal 1-year outcomes could be achieved despite aEEG abnormalities

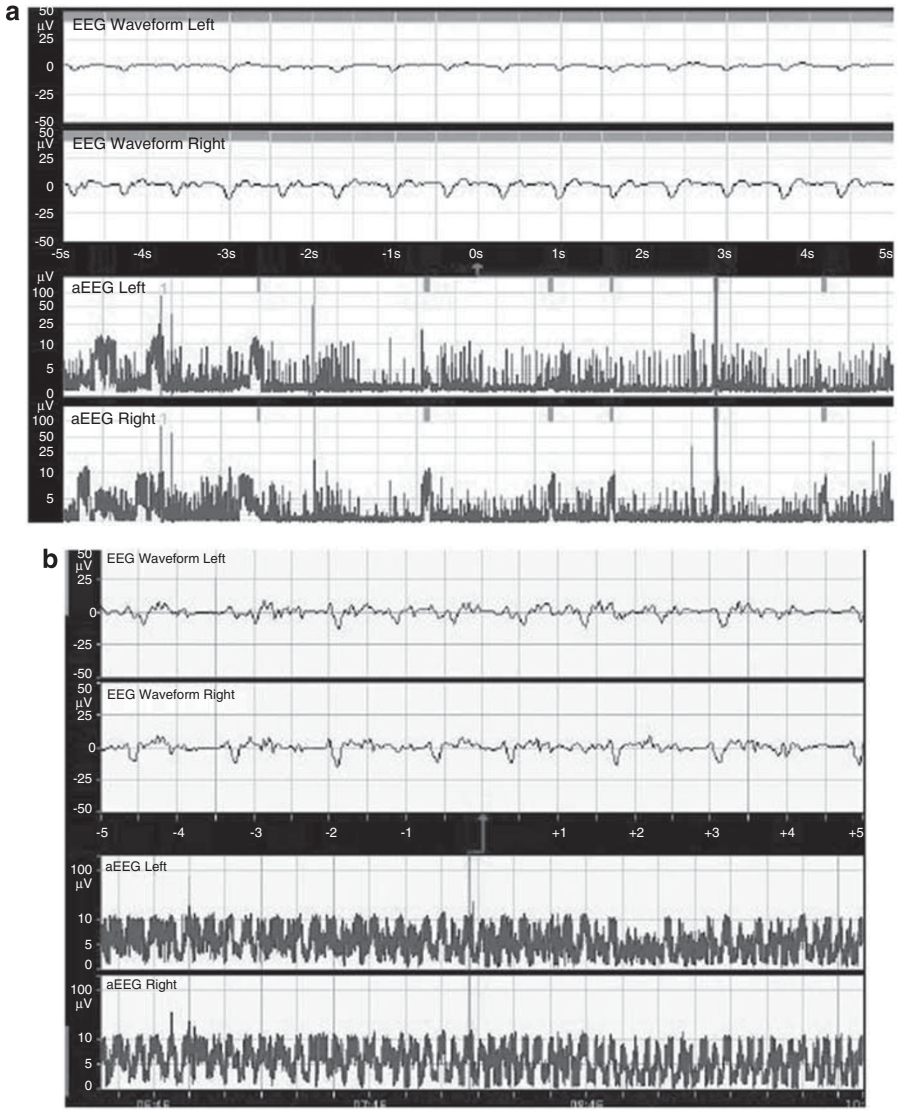

Figure 4 (**a**) Several discrete seizure episodes (shaded or orange bars) on a background of burst suppression; seizures clearly show an abrupt rise in both upper and lower margins. (**b**) Status epilepticus: multiple marked seizure events dominating nearly the entire tracing. The color reproduction of the figure is available on the html full text version of the paper. aEEG, amplitude-integrated EEG; EEG, electroencephalography.

persisting after 24 h.[38] Further research into the effects of hypothermia on the evolution of aEEG after HIE is ongoing.

aEEG in the preterm neonate

Although the application of aEEG to term infants is widely accepted, its use in preterm infants continues to be an active area of research. Over the last two to three decades, literature concerning normal and abnormal patterns and their clinical usefulness in this population has emerged. Several key studies characterized cerebral function for infants >30 weeks.[22,39] Compared with term infants, the background pattern of less mature infants is more discontinuous. There are more frequent 'bursts', and the raw tracing of the EEG signal may show periods of relatively low voltage with sudden but infrequent bursts of high activity. Burdjalov *et al*.[40] developed a quantifiable scoring system for brain maturation based on aEEG. Using four distinct variables—continuity, cyclicity, bandwidth and lower border amplitude—scores from 0 to 13 were obtained and compared with gestational ages (GAs). As an objective method, this system indicated that all variables as well as total score increased with increasing GA.

In the last 5 to 10 years, attempts have been made to accurately describe the tracings of healthy extremely low birth weight infants, or those <32 weeks gestation without brain injury.[41–46] Olischar *et al*.[43] determined reference values of aEEG tracings in such infants, and characterized their background patterns as continuous, discontinuous high voltage and discontinuous low

voltage. By monitoring this population over the first two weeks of life, this study showed that the amount of continuous activity increased with higher GA, whereas the amount of discontinuous activity decreased with higher GA. This effect is only one example of extrauterine influences on postnatal maturity. Prospective studies of very preterm infants monitored over several weeks showed that the aEEG pattern matured not only with higher GA, but with postmenstrual age (PMA) as well.[44,45] In fact, at comparable post-conceptional ages, infants with higher PMA have more mature patterns than those with lower PMA, despite a lower GA.[47]

Just as in term infants, evidence of cyclicity is important in preterm babies. However, relatively fewer studies have examined this phenomenon by aEEG and its impact on outcome, and even fewer have investigated cyclicity in extremely premature infants. Many studies use cycling criteria as part of their quantitative or qualitative classifications.[43,44,47] Cycling was typically defined as regular variations of activity and amplitude lasting at least 20 min. The amount of time spent in quiet sleep decreases as infants mature.[48] This same study examined the effect of the Newborn Individualized Developmental Care and Assessment Program on sleep, and discovered no change in the amount of time spent in quiet sleep of those who received this specialized care. In cEEG, SWC is observed in those <30 weeks, but appears to be more disorganized.[24] In aEEG, cyclical variations were noted at a mean GA of 28 weeks in similarly immature infants.[49] Discrimination of sleep states may begin as early as 25 to 26 weeks.[50] Whether the duration of active versus quiet sleep and the timing of cycling onset can provide prognostic information in this group of infants remains to be seen.

The application of aEEG in the setting of seizures and brain injury in preterm infants has proven to be extremely valuable. A recent study has shown that electrographic seizures in the first week of life correlate with adverse outcomes.[3] Intraventricular hemorrhage (IVH) and its subsequent effects, specifically, influence a number of aEEG characteristics. When compared with age-matched controls, premature infants <30 weeks of GA with IVH show increased discontinuity, seizures and decreased amount of SWC.[51] This effect was more pronounced in patients with more significant bleeding. Similar results are found in infants that progress to post-hemorrhagic ventricular dilatation (PHVD), and findings on aEEG could be seen even before clinical signs of increased intracranial pressure were apparent.[52,53] A recent study prospectively examined infants with PHVD before and after cerebrospinal fluid drainage by placement of an external ventricular device. Decreased continuity and burst suppression were noted with progressive PHVD, and these findings improved significantly in the majority of patients after external ventricular drainage device placement.[53]

Other aEEG indicators may be used to determine the significance and perhaps prognosis of brain injury in preterm infants. Increased burst rate and an earlier onset of cycling are associated with better outcomes, and burst rates $<130\,h^{-1}$ are associated with poorer outcomes.[54] The use of these tools on early aEEG examination may help in providing useful counseling information. Interburst interval, the quiescent period of isoelectric activity measured on the raw unprocessed signal, is increased in infants with brain injury and may predict handicap at 2 years of age.[55] Similarly, lower spectral edge frequency may indicate the severity of those with white matter injury.[56]

Medications and artifacts

Many of the medications used in the NICU may affect the aEEG tracing. Antiepileptic drugs and opioids are most commonly given to both term and preterm babies, and generally cause a transient depression in the overall activity of the aEEG. Phenobarbital, for example, is often a first-line medication for the treatment of seizures. Its role as a central sedative and antiepileptic drug causes decreased cerebral activity, generalized voltage suppression and increased interburst interval.[45,57,58] Morphine and midazolam similarly have been shown to exert similar effects on aEEG, [45,57,59–61] and these changes were reversed on administration of naloxone.[59] Surfactant, administered to babies for respiratory distress, causes a decrease in cerebral activity and a significant decrease in burst rate on aEEG.[62,63] Interestingly, more than half the patients in this study received phenobarbital during mechanical ventilation for sedation purposes. Osredkar demonstrated a delay in SWC onset when babies were given three or more anticonvulsant drugs.[23]

The difficulty in interpreting and applying aEEG in clinical practice rests heavily on the distinction between artifact and activity. The range of recorded artifact varies anywhere between 12 and 60% among published values;[64,65] both of these numbers were obtained with the assistance of the raw EEG tracing. Electrocardiogram activity, patient movement, high-frequency oscillator ventilation and electrode placement are a few of the variables that may influence the presence of artifact. One of the more common signs seen from electrocardiographic artifact is the 'drift of the baseline' effect, in which the baseline tracing becomes falsely elevated in the setting of severely suppressed background activity. A baseline level above 5 μV may be mistaken for a more reassuring pattern. A few more examples of artifact tracings are detailed and described in Figure 5. Owing to these apparent difficulties with interpretation, nonexperts with only a small amount of exposure may over- or underanalyze certain events.[66] Further training is necessary and advocated.[67]

Conclusion

With the increasing use of aEEGs in many NICUs around the world, ongoing education and research are necessary. The literature

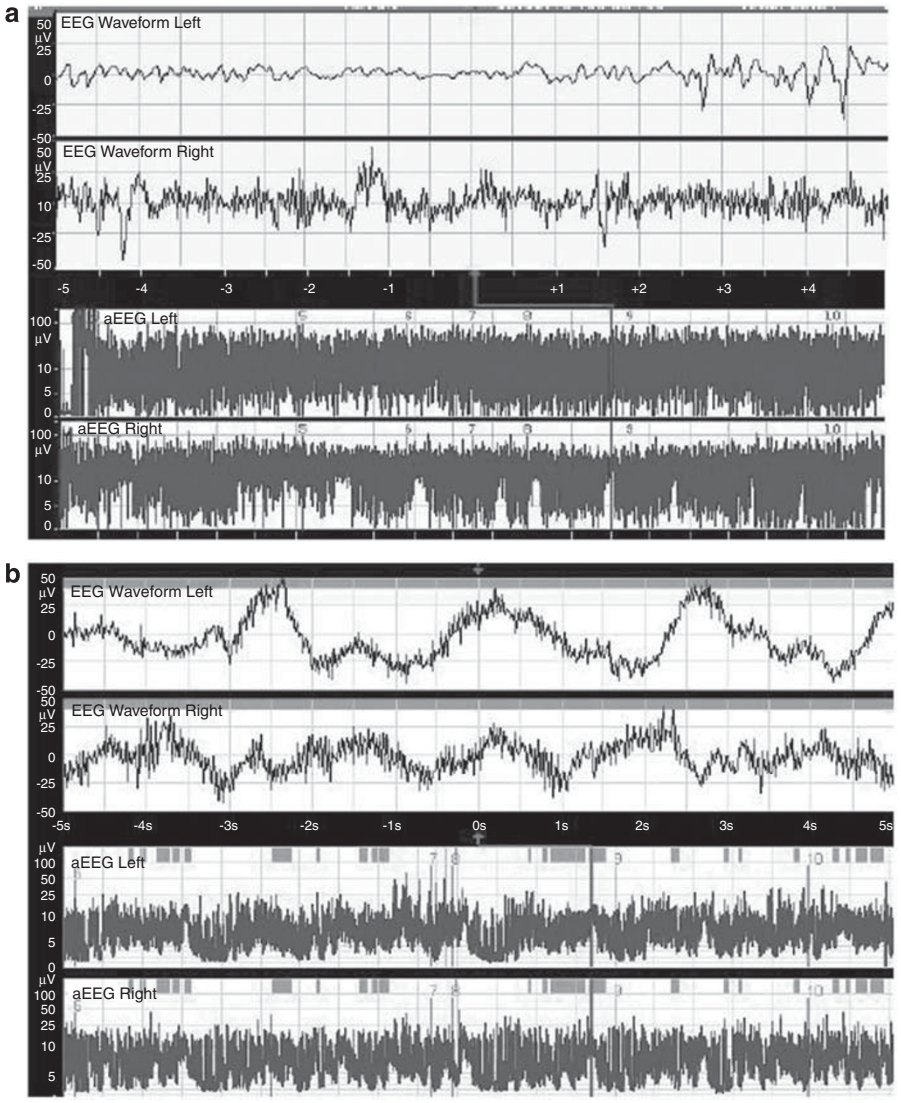

Figure 5 (**a**) High-frequency oscillatory ventilation (HFOV) may cause significant artifact resembling seizures. Correlation with the raw electroencephalography (EEG) tracing above is essential. (**b**) A similar effect is seen from muscle artifact in both hemispheres. aEEG, amplitude-integrated EEG.

on term infants is well established, with an emphasis on encephalopathy and seizure monitoring. The impact of hypothermia as a neuroprotective strategy on aEEG, however, is still unclear. Research on preterm infants is promising, especially in the settings of maturation and brain injury. Although there are no evidence-based indications for its use in this population yet, the information made available by aEEG has provided insights into early identification of brain injury. Medications, other neonatal intensive care interventions and their influence on brain activity also remain an area of great interest. Many centers without the availability of conventional video-EEG could benefit from the clinical application of this device in the NICU. As a result, the promise and reward of aEEG will be increasingly evident, and our approach to the developing brain will continue to evolve.

Conflict of interest

The authors declare no conflict of interest.

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