

Quantitative Electroencephalographic Changes With Apnea In Preterm Infants

J Tallapragada, D Washburn, D Mandelbaum, M Hiatt, T Hegyi

Citation

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Abstract

Objective: To investigate potential changes in the spectral distribution of absolute power of Quantitative Electroencephalographic (QEEG) recordings from preterm infants with apnea of prematurity.

Methods: The QSI 9000 electrodiagnostic system was used for quantitative analysis and topographical mapping of spectral data. In five infants (birth weight 970 1559g; gestational age 26 31 weeks tested at 28 36 weeks) we recorded 30-minute QEEG segments. We divided the EEG into four time groups 1) Preapneic period obtained 1 3 minutes before the apneic episode, 2) Apneic period averaging 15 seconds, 3) Post apneic period lasting for three minutes and 4) Baseline (BL) control EEG that was free of an apneic event for at least five minutes. These four groups together were defined as one "event". The apneic events were documented by a cardiorespiratory monitor and by visual inspection. The spectral distribution for each group was divided into 2.5 second epochs and the absolute power for five frequency band passes was calculated: Delta 1 (0.4 2.0 Hz), Delta 2 (2.0 4.0 Hz), Theta 1 (4.0 6.0 Hz), Theta 2 (6.0 8.0 Hz) and Alpha Beta (8.0 26 Hz).

Results: Significant differences were found in twelve out of fifteen events (consisting of preapneic, apneic and postapneic episodes) compared with the corresponding baseline period ($p < .01$). Nine of 15 combined apneic and post apneic episodes were also significantly different from baseline levels. Significant differences were noted in Theta 1 and Theta 2 bands.

Interpretation: These results suggest that apneic events in preterm infants alter the EEG during the episode and for at least the subsequent three-minute period.

ABBREVIATIONS

QEEG -Quantitative Electroencephalogram

Hz- Hertz.

REM - Rapid Eye Movement

INTRODUCTION

Apnea is a common disorder of prematurity. It may be associated with a number of underlying disorders including sepsis, hypoxia, intracranial hemorrhage or metabolic aberrations [1] or occur in their absence as a result of an immature respiratory drive [2]. It has been suggested that the immaturity of the brain stem centers that regulate breathing may be a major underlying factor [3], a hypothesis supported by prolonged brainstem auditory conduction times in infants with apnea [4].

Normal brain maturation and aberrations in the progress of the normal maturational sequelae have been traditionally

studied by standard electroencephalographic (EEG) examinations. However, the information obtained from the traditional EEG is limited as compared to the new neuroimaging techniques. Computerized tomography and magnetic resonance imaging are essential in the diagnosis of structural pathology while positron emission tomography (PET) and cerebral blood flow (CBF) studies can demonstrate functional changes.

Over the last two decades advances in computer technology have led to an evolution in EEG studies. It is possible to plot the potential fields of EEG on a topographical model of the scalp. This non invasive neuroimaging technique called quantitative EEG (QEEG) or topographic brain mapping permits the visualization of both structural and functional processes of the brain. The computer analyzes and quantifies the EEG, plots it out in a compact and comprehensible manner, and employs statistical tests to give significance to

the analyzed data, thus providing a comprehensive understanding of the electrical waveforms and their display.

The aim of this study was to investigate potential changes in QEEG recordings associated with apnea in preterm infants. The study was performed to understand whether apnea of prematurity can result in changes in the EEG, which may, thereby be looked at by the unique ability of QEEG to quantify aspects of the record and obtain information about potential cerebral functional changes. We also wanted to note any progression of these potential changes with subsequent apneic spells in the same infant.

METHODS

Infants suffering from apnea of prematurity were eligible for inclusion into the study. Those excluded from consideration were infants with congenital anomalies and intraventricular hemorrhage. All of the study infants were on theophylline therapy. The Institution Review Board approved the study and informed consent was obtained from the infant's parent or guardian. The infants were studied after transfer to a specially designated room, the neurophysiology laboratory, to minimize external interference and artifacts in records of EEG.

EEG was recorded with a QSI 9000 electrodiagnostic system that provides quantitative analysis and topographic mapping of spectral data. A full 19 lead configuration of scalp electrodes with linked ear reference and electrooculogram electrodes to detect eye movement [following 10 20 international system] was implemented after the scalp was prepared with omniprep and conductive gel. Recording of the channels took place during quiet sleep as determined by the clinical observation of the patient. EEG was recorded after feeding the baby to obtain artifact free recording without the use of sedation. The apneic event was documented by a cardiorespiratory monitor and by visual inspection. At least 30 min QEEG segments including periods of apnea were recorded on each infant and stored on optic disc for analysis. Oxygen saturations were monitored simultaneously on all these infants with the help of a pulse oximeter.

The basis of QEEG is 'Spectral Analysis' or Fourier analysis, which converts time series signal into frequency spectral components present in the signal. The data can either be evaluated in the time domain, relating time and electrical potential as in a traditional clinical EEG or in the frequency domain, which permits analysis of the frequency components of the signal. The EEG traces are then converted

by 'Power spectral analysis' into power spectra. This enables the data to be measured in terms of square microvolts within a frequency band or microvolts square/ Hertz (HZ) when measured along a continuous frequency axis. Power spectral analysis for the quantification of EEG thus yields 'absolute power' and asymmetry in power for different frequency band passes. We define absolute power as the power that is derived directly from the power spectrum as described by various investigators [5,6,7,8]. Topographic mapping is the visual display of this data as a color coded spatial mapping of actual distribution of the power or asymmetry of power in the frequency domain. These maps may be constructed for broadband activity or for selective frequency components. The color scale denotes the ranges present.

Apneic episodes (Table 1) were analyzed by dividing EEG tracings into four periods in relation to apneic episodes as follows:

- 1. Preapneic period obtained 1 3 minutes before the apneic episode
- 2. Apneic period averaging 15 seconds and ranging from 2 63 seconds
- 3. Postapneic period lasting for 3 minutes post apnea, and
- 4. Baseline control period obtained from an EEG that was free of an apneic episode for at least five minutes.

Figure 1
Table 1: Subject Population

Gest Age Rate (weeks)	Birth Weight (grams)	Postconceptional Age (weeks)	Apneic Episodes (n)	Apnea Duration (seconds)	Oxygen Sat. (%)	Heart (bpm)
26	97	30	1	25	80	77
27	1130	28	2	6-8	82-95	78-80
28	1260	36	1	4	95	119
30	1320	34	5	12-63	70-99	70-180
31	1559	36	6	11-22	74-85	72-142

These four periods together comprise an “event”. A total of 15 such combined events obtained from the apneic episodes listed in Table 1 from all study infants were analyzed by obtaining the spectral distribution for 2.5 sec epoch in each period selected artifact free and calculating absolute power for five frequency band passes. Since the neonatal EEG is largely composed of delta and theta activity with a relative paucity of faster rhythm of alpha and beta activity, delta and theta bands were further broken down into their sub components while alpha and beta bands were combined together. The frequency bands that were studied were as

follows: Delta 1 [0.4 2 Hz], Delta 2 [2.0 4.0 Hz], Theta 1 [4.0 6.0 Hz], Theta 2 [6.0 8.0 Hz] and alpha beta [8.0 26.0 Hz].

Individual means and variances of the absolute power were calculated for each channel, in the five frequency band passes for the epochs selected from each of the periods. Maps were made for the sum of the means in each period and comparisons were made for the extent of differences between these periods by means of t statistic. The absolute power for the five-frequency band passes in each of the preapneic, apneic and postapneic periods were individually compared to their corresponding baseline control period. A t statistic topographic map was obtained for these comparisons. A p value of < 0.01 was considered to be statistically significant. The results were displayed as topographic maps of t test denoting the range of significance by means of color scale.

RESULTS

Twelve infants were studied during an 18-month period. Seven were excluded from the analysis because the manifestations of apnea identified in the intensive care nursery disappeared after transfer into the special study area. Therefore the final group was comprised of five infants with apnea of prematurity ranging in birth weight from 970-1559 grams, in gestational age from 26-31 weeks and in post-conceptional age from 28-36 weeks. The duration of apnea, number of apneic episodes in each infant, the heart rate and oxygen saturation during each episode and characteristics of the study group are all as shown in Table 1. Infants were stimulated either by mild tactile stimulation, flow oxygen or by bagging with bag and face mask to terminate the apnea depending on associated bradycardia of less than two thirds of the baseline heart rate or desaturations less than 85% for more than five seconds or associated with color changes. The one infant noted to have had an apneic episode of 63 seconds had shallow breathing by visual inspection but was documented as apneic episode by the cardiorespiratory monitor. The infant had no significant desaturations associated with the episode and responded to mild stimulation for an associated bradycardia of 100-110/ minute during the episode.

Statistically significant differences were found in 12 out of 15 combined events [$p < 0.01$] that were analyzed, obtained from all study infants as described previously. There was an increase in absolute power in theta & delta frequency bands in apneic and post apneic periods when compared individually to their baseline period. Preapneic period was

not significantly different from the baseline period. Since QEEG data was similar for apneic and post apneic periods, these were combined and compared to the base line. Significant differences [$p < 0.01$] were noted in 9 out of 15 comparisons. Topographic investigation of individual band passes in each comparison revealed significant differences in theta 1 and theta 2 bands in each of the analyses. Also, there was a trend for increased power in theta and delta bands with a further increase in this trend with subsequent apneic episodes.

DISCUSSION

A number of changes in brain electrical activity occur with maturation [10,11]. In addition, behavioral states also affect the EEG of the newborn. Gasser et al have used the changes in EEG with age as a technique for quantifying the normal development of the central nervous system. They showed that absolute power decreased with age in all bands except alpha and that with maturation of the brain a shift in the power towards higher frequencies could be seen [12]. Steraide et al have studied neuromodulatory systems and found them to be capable of shifting thalamocortical neurons between different slow and fast oscillatory states in the sleeping and aroused brain. They also showed that slow frequencies are noted to appear on the EEG during quiet sleep and are seen to be modulated by various neurotransmitter systems that innervate the brainstem, forebrain and the posterior hypothalamus. They suggest that the changes in oscillatory activity of the brain may be indicative of changing states of underlying neural circuits [13]. An over abundance of slow wave activity may relate to such conditions as infarcts or tumors as studied by Nuwer and Duffy [6,7].

Several workers have used clinical EEG as a prognostic indicator in preterm and term infants with various neurologic insults [14,15]. Apnea can result in brain injury secondary to accompanying hypoxemia and ischemia. Several investigators have studied the effects of apnea on clinical EEG. Deuel observed marked suppression of EEG during apneic spells, which could possibly be due to cerebral hemispheric or diencephalic dysfunction. By polygraphic monitoring of apneic spells, she noted differences between different durations of apneic spells. Short apneic spells did not relate to age or EEG maturation. They seemed to be an extension of the periodic respiratory pattern commonly found during the quiet sleep of prematures at certain levels of maturity and may be associated with tracé alternans EEG pattern that is common at gestational ages above 36 weeks.

Prolonged apneic spells differed in mechanisms of production from patient to patient and could be due to causes like seizure disorder, pulmonary insufficiency and cerebral anoxia [16].

Fenichel et al noted mild amplitude suppression of the EEG during episodes of non convulsive apnea. The presence of EEG suppression was not associated with the duration of apnea. Also prolonged apneic spells without bradycardia suggested the possibility of a convulsion where as non convulsive apnea of 20 seconds or longer was nearly always associated with bradycardia [17].

Jensen et al studied the effect of hypoxia on EEG activity in rats of varying gestation exposed to varying degrees of hypoxia from 0.4% O₂ until the onset of apnea and bradycardia. EEG was recorded before, during and after the hypoxic exposure. Epileptogenic effect of hypoxia was seen in the immature brain more than in older animals where hypoxia resulted in an isoelectric EEG [18].

Nishimura and Maeda analyzed spectral characteristics of EEG in a newborn at steady state and during central sleep apnea. At 6 minutes before sleep apnea disturbance of regulated rhythm of respiration and suppression of spectrum of nearly 10 Hz of EEG with irregularity was noted. During sleep apnea the spectrum of EEG more than 5 Hz disappeared and it was irregular. During recovery from sleep apnea this disorder in the spectrum of EEG decreased gradually and the regular spectrum appeared showing that the spectrum of EEG is in the process of returning to steady state. According to this study it is possible to predict several minutes before sleep apnea. The causes of this phenomenon are considered to be due to lack of stimulus transmission because of underdeveloped higher centers and autonomic nervous system. It was also thought that the sleep apnea causes an obstacle in circulatory system and a delay in the feed back loop between respiratory and vasochemoreceptors [19].

Reimao studied power spectral analysis of EEG samples from 2-10 min of each stage of 1st REM cycle in elderly patients with excessive daytime sleep disorders and obstructive sleep apnea syndrome. The percentage power in relation to total EEG power was determined for delta, theta, alpha and beta frequency bands. It showed a tendency to decrease from the slowest to fastest frequency bands in every sleep stage. Percentage power distribution in the delta range increased progressively from stage 1-4. REM levels were between stages 1 & 2 [20].

In our study, the infants studied were of different gestational and post conceptional ages. Chronologically, several EEG changes are seen during development. But the majority of these changes are seen from 32 weeks gestational age and beyond. Most of the premature infants are noted to have mostly the slow wave activity with alternating REM and non REM sleep. Due to these reasons and also because Idiopathic apnea of prematurity is noted in the gestational ages that are included in our study, the study infants were selected among this group. Well, healthy term infants EEG cannot be used and compared as controls to the EEG in preterm infants, as previously explained. So, it was best thought to obtain adequate controls from Abaseline normal EEG obtained during the nonapneic periods from the same infants to be compared to their own EEG recordings during apneic periods.

The limitation of our study was a small population of preterm infants that may not accurately validate the results that were obtained. Although the study was non invasive, due to the complex nature of transfer of already compromised preterm infants to the neurophysiologic laboratory, and the associated unpredictability of apneic episodes happening after transfer, resulted in the paucity of infants included in the study. Several of these infants in the laboratory did not have any apneic episodes. In some infants EEG could not be recorded due to absence of quiet sleep, whereas in some others, the episodes and the recording had to be terminated as the infants became unstable.

CONCLUSION

We investigated quantitative EEG changes associated with apnea in premature infants with “Idiopathic apnea of prematurity”. Our results showed significant differences between the apneic episodes and the base line EEG with an increase in absolute power in theta and delta frequency bands, with similar results in the immediate post apneic period. A further increase in the absolute power in the same frequency band passes was noted with subsequent episodes in the same infant. Our results suggest that apneic events in premature infants significantly alter the EEG during the episode and for at least the subsequent three-minute period. Preapneic EEG was not different from baseline EEG and was not predictive of apneic episodes.

The increased slow wave activity that is observed in our study could mean possible extension of periodic breathing pattern found during quiet sleep in premature infants or a possible effects of apnea due to accompanying hypoxemia,

as shown in the studies of Deuel and Jensen et al [16,18]. These effects were evidenced by mild amplitude suppression in clinical EEG and increased percentage power in delta range in power spectral analysis in the previous studies [17,20].

The possible effects of hypoxia on apnea and its association with bradycardia have to be further evaluated by us with the available data. In order to validate these conclusions further studies with larger patient population are warranted.

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CORRESPONDENCE TO

Thomas Hegyi, M.D.
Robert Wood Johnson Medical School
One Robert Wood Johnson Place, MEB 312C
New Brunswick, NJ 08903-0019

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Author Information

Jyotsna K. Tallapragada, M.D.

Division of Neonatology, Department of Pediatrics, UMDNJ-Robert Wood Johnson Medical School

Donna Washburn

Division of Neonatology, St. Peter's University Hospital

David Mandelbaum, M.D., Ph.D.

Division of Neonatology, Department of Pediatrics, UMDNJ-Robert Wood Johnson Medical School

Mark Hiatt, M.D.

Division of Neonatology, St. Peter's University Hospital

Thomas Hegyi, M.D.

Division of Neonatology, Department of Pediatrics, UMDNJ-Robert Wood Johnson Medical School