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Comparison of Cerebral and Peripheral Tissue Oxygenation Index (TOI) Measured with Spatial Resolved Near Infrared Spectroscopy

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Statement of problem: Spatial-resolved near-infrared spectroscopy enables non-invasive continuous measurement of “tissue oxygenation index” (TOI), which correlates to mixed venous oxygenation (SvO2). The aim of the present study was to compare cerebral TOI and peripheral TOI.

Statement of methods: Repeated simultaneous measurements on right forehead and calf, were performed in 10 neonates with gestational age (GA) >32 weeks within the first two days after birth by reapplying the NIRS optodes five times. All patients were stable without respiratory or cardio-circulatory support.

After each reapplying procedure TOI values of five 15-seconds periods were analysed. On calf in addition SvO2 was calculated with NIRS and the venous occlusion method. TOI values of calf were included for further analysis, when differences of obtained TOI and SvO2 (%) values were <3.

Heart rate, peripheral arterial oxygen saturation, central and peripheral temperatures were measured continuously. Arterial blood pressure was measured before and after measurement procedures.

Summary Results: The ten neonates had a mean gestational age of 35.9±4.4 weeks, a mean birth weight of 2350±780 and mean postnatal age of 18.2 ±18.8 hours. All cerebral TOI measurements and 4±2 measurements/neonate of peripheral TOI were included for further analysis.

Cerebral TOI (70.3±3.5%) was significantly higher (p=0.036) than peripheral TOI (63.9±8.3%). Peripheral SvO2 of calf was 65.4±7.9%.

Implications: Cerebral TOI is significantly higher than peripheral TOI in neonates with gestational age > 32 weeks.
Automatic Detection of “Delta-Brush” and Induced Heart Rate Changes in Preterm Infants

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Objective: The aim of this work was to study the relationship between delta-brush and induced heart rate (HR) changes in preterm infants. Delta brush is a high frequency (8-20Hz) spindle-like activity superimposed on 1-3Hz delta waves (Eyre 1988). During quiet sleep in preterm infants induced HR changes in form of an acceleration (lasting about 6 seconds) are closely linked with the occurrence of slow-wave EEG bursts (Pfurtscheller et al. Brain Dev. 2005).

Methods: A group of 10 preterm infants with conceptional age (CA) of 36.55 ± 1.25 (mean ± SD) weeks was studied. From long-term EEG and ECG recordings, periods of about 15 min with low HR variability and slow-wave bursts were selected. From the raw EEG (0.5-100Hz) two data sets were generated, one by high-pass filtering (5Hz) and the other by low-pass filtering (4Hz). All 3 data sets (original, 0.5-4Hz and 5-100Hz) were subject of an automatic burst detection method with the goal to search for slow-waves and delta brush, respectively. In addition to automatic EEG burst detection also induced HR changes were analysed synchronously to EEG bursts.

Results: Delta brush is accompanied by a HR acceleration in the order of about 1-3 bpm, similar as found during the occurrence of slow-wave bursts (Pfurtscheller et al. Brain Dev. 2005).

Implications: Independent detection of slow-waves and delta brush in discontinuous slow-wave EEG of preterm infants may give new insight in maturational processes.

This work was supported by “Land Steiermark” (project A3-16B74-05/1).

The preterm infants were studied at the Neonatal Intensive Care Unit (NICU), Department of Pediatrics, Medical University of Graz, Austria. The analysis was done at the Institute for Knowledge Discovery, Laboratory of Brain-Computer Interfaces, Graz University of Technology, Austria

References:
Heart Rate Changes Time-Locked to Slow-Wave EEG Bursts in Preterm Infants at 36 Weeks of Conceptional Age and Maturational Aspects

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Objective:
Normative data and maturational aspects of cortico-cardiac coupling mechanisms during periods of discontinuous EEG are presented in a group of healthy preterm infants at 36 weeks conceptional age.

Methods:
A group of preterm infants with a conceptional age (CA) of 35.9 ± 0.6 weeks (mean ± SD) was studied. From long-term EEG and ECG registrations, sections with a length of about 10 minutes with low heart-rate (HR) variability and discontinuous slow-wave EEG bursts were selected and further analysed. After an automated detection of slow wave bursts, the corresponding instantaneous HR trials were averaged.

Results:
Healthy preterm infants showed a HR increase, time-locked to the occurrence of slow-wave bursts during discontinuous EEG. At 36 weeks of conceptional age the HR displayed an acceleration of 2.5 ± 1.4 bpm (mean ± SD) whereas in the EEG the burst-to-burst-interval (BBI) was 13.2 ± 2.2 s (mean ± SD). There seems to be a minor acceleration in infants of 32 weeks CA.

Implications:
These normative data of healthy preterm infants are important for the study of maturational aspects of the brain and might help to differentiate between normal and abnormal brain function in preterm infants.
Treatment of Refractory Neonatal Electroclinical Seizures with Continuous I.V. Infusion of Midazolam

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Statement of the problem: 40% of the neonatal seizures are refractory to drug treatment. In Romania, i.v. Phenobarbital is not available on a large scale. These made our group decide to investigate alternative treatments of refractory seizures. Another aim of the study was to investigate the role of aEEG in monitoring anticonvulsant treatment.

Material and methods: This is a pilot study. In the study were included 11 cases that presented clinically with multifocal clonic seizures that had electroencephalographic equivalent on aEEG: 5 term neonates with perinatal asphyxia, one term newborn with subarachnoid hemorrhage, one 36 weeks large for gestational age newborn with intraventricular hemorrhage grade III Papile with post-hemorrhagic hydrocephalus, one 29 weeks newborn with perinatal asphyxia and periventricular leucomalacia that presented with seizures at 3 weeks of age and one 32 weeks neonate with hydrops due to hemolytic disease. All the patients had normal blood glucose and electrolytes at the time of the seizures. The patients were treated with a loading dose of 20 mg/kg Phenobarbital, then Phenytoin loading dose of 20 mg/kg and maintenance dose of 5 mg/kg/ day and if the seizures were not stopped Midazolam 0.04 mg/kg/hour as continuous infusion (in one case the dose was increased to 0.1 mg/kg/hour).

Results: In all the 10 cases, the seizures were not stopped after the treatment with Phenobarbital and Phenytoin and needed treatment with Midazolam continuous infusion. In all the patients, both the clinical and electric seizures were stopped after the use of continuous infusion of Midazolam. The dose of Midazolam was decreased to half 24 hours after the disappearance of both electrical and clinical seizures and the normalization of the aEEG. The aEEG tracing normalized after 1 to 2 days. The i.v. was stopped after 24 hours of normal aEEG tracing and no clinical seizure activity. Phenytoin was stopped the day after the termination of the Midazolam treatment. The seizures did not re-appear either clinical or electroencephalographic.

Implications: Continuous infusion of Midazolam is an effective anticonvulsant treatment in the case-series presented. The aEEG monitoring of the cases allowed the bedside monitoring of the brain activity and the adjustment of the treatment based on this. Based on these findings, a study comparing the effects of Midazolam continuous i.v. and classic (Phenobarbital and Phenytoin) treatment will be conducted. This case-series also shows the importance of brain monitoring with the help of aEEG during the treatment of neonatal seizures.
Effect of Theophylline on Amplitude-Integrated EEG in Preterm

Patrizia Kutz, Sabina Backendorf, Sirma Supcun, Claudia Roll

Background/Aim: Methylxanthines are routinely given to avoid apnoea in preterm infants. Here, we investigated the effect of theophylline administration on aEEG activity in preterm infants.

Patient and Methods: In 19 preterm infants, gestational age 27 (23-30) weeks [median, range], birth weight 800 (480-1150) g, a theophylline loading dose of 6mg/kg was administered intravenously over 30 min, and aEEG, heart rate, oxygen saturation and pCO₂ were registered continuously from 1 hour before to 1 hour after theophylline administration. Infants with an aEEG impedance rise > 5 kΩ or simultaneous administration of sedatives were excluded. Average values during 1 h before and 1 h after theophylline calculated for each infant were compared by the Wilcoxon signed rank test.

Results: Of the 19 infants studied, 4 were excluded for rise of impedance, and 1 because of co-administration of phenobarbitone. In the remaining 14 infants, the average aEEG amplitude rose from 40.3 (16.3-54.8) to 46.8 (36.4-57.7) units (p<0.01), while heart rate rose from 146 (131-175) to 152 (135-187) bpm (p<0.05). Impedance, oxygen saturation and pCO₂ remained stable.

Conclusions: Theophylline increases cerebral cortical activity in preterm infants.
Introduction: The prevalence and characteristics of acute seizures in children undergoing therapeutic hypothermia following pulseless cardiac arrest are unknown. A high proportion of seizures may be subclinical and paralytic medications required by hypothermia protocols may mask them; therefore, diagnosis requires electroencephalography. Despite the advantages of continuous, full-array, video-EEG monitoring, neurophysiologists only interpret them intermittently, limiting the ability of intensivists to make real-time EEG-based seizure treatment decisions. Amplitude-integrated EEG (aEEG) and density spectral array (DSA) may assist seizure detection by intensivists. We hypothesize that seizures are common during therapeutic hypothermia following in-house cardiac arrest in children and that aEEG and DSA will be sensitive and specific for seizure detection.

Methods: We performed a prospective, pilot observational study of 5 consecutive children undergoing continuous EEG monitoring during hypothermia (24 hrs), re-warming, and then an additional 24 hrs. Electrographic seizures were identified and seizure burden (% time occupied by electrographic seizures) was calculated for the first 10 min of each hour. Four channels of aEEG and DSA were generated from full array EEG (right & left, frontal & posterior). Six hour segments were scored as “seizures” or “no seizures” by a neurophysiologist reading full array video-EEG monitoring, a neurophysiologist aEEG and DSA reader, and an intensivist aEEG reader.

Results: Mean age of study subjects was 25 months (range 2-44 months). A total of 359 hrs of EEG were reviewed with a standardized seizure-scoring protocol by a neurophysiologist. Seizures occurred in 2/5 patients. One had onset during hypothermia, escalating to frequent recurrent seizures (55% seizure burden) evolving into status epilepticus lasting over 24 hours. Another had onset of seizures during re-warming and experienced recurrent brief seizures (18% seizure burden) followed by seizure termination. Seizures were not preceded by inter-ictal spikes or sharp waves. All were subclinical and bi-hemispheric at onset or rapidly secondarily generalized. Seven of 48 (21%) six-hour epochs contained seizures. Compared to video-EEG monitoring, aEEG seizure interpretation by a neurophysiologist versus intensivist had a sensitivity of 78% vs. 78%, specificity of 82% vs. 77%, positive predictive value (PPV) of 50% vs. 43%, and a negative
predictive value (NPV) of 94% vs. 94%. Compared to video-EEG, DSA seizure detection by a neurophysiologist had a sensitivity of 78%, specificity of 82%, PPV of 50%, and NPV of 94%.

**Conclusions:** Subclinical seizures were common during therapeutic hypothermia after cardiac arrest. aEEG and DSA were reasonably sensitive and specific for identifying 6 hour periods which had “seizures” versus “no seizures”. With a high NPV, aEEG was effective in “ruling out” seizures. The lower PPV suggests that some artifacts may be misidentified as seizures. These preliminary findings suggest that bedside interpretation of aEEG/DSA may be useful to guide post-resuscitation seizure management of children, but confirmation by conventional EEG may be required. Further studies of seizure prevalence, their predictors, prognostic significance and detection using aEEG/DSA are warranted.
Correlation of Amplitude Integrated EEG with Conventional EEG in Premature Babies

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The study was supported by the National Institute for Psychobiology in Israel and the Israeli Clinical Pediatric Society

Background
Neonatology is one of the most rapidly progressing fields in medicine with a dramatic improvement in the survival of premature babies. These babies are exposed to different brain insults such as intraventricular hemorrhage (IVH), periventricular leucomalacia and meningitis. While cardiorespiratory status is routinely monitored in the Neonatal Intensive Care Unit (NICU) cerebral function monitoring has lagged behind.

Conventional electroencephalography (EEG) has specific features in premature infants. Abnormalities were correlated with cerebral insults and abnormal outcome, but in spite of these properties routine use of conventional EEG has not gain favor since it is cumbersome, interfere with the care of infants and need expertise for interpretation. Amplitude integrated EEG (aEEG) is a method that samples EEG signals from two parietal electrodes. The technique is user friendly and easy to interpret. Studies done on term infants after birth asphyxia and for monitoring seizures activity with aEEG established an important role for the aEEG in neonatal units for these indications. Studies in premature babies on normal patterns and on the prognostic significance of abnormal patterns in babies with IVH suggest that this device can also be used as a monitor in premature babies. Adults and term neonates comparisons of aEEG with conventional EEG were published, but still no study compared simultaneous conventional EEG with aEEG in premature infants at different gestational ages.

Objective: To correlate aEEG with conventional EEG in premature infants using features of continuity and amplitudes of both modalities at different gestational ages

Methods
Infants born between 24 and 39 weeks reliable gestational age with no major congenital malformations were prospectively enrolled in the study. Ninety to 120 minutes of simultaneous aEEG, conventional EEG and video were recorded in the first two weeks of life and once every two to three weeks until discharge or 39 weeks gestation.
EEG recordings were divided into 10 minutes period and for each such period the lower and upper border voltage of the tracing were visually assessed, then average voltage and amplitude were calculated (MinCFM, MaxCFM, AvCFM and AmpCFM respectively).

EEG recordings were assessed visually and with specially devised software. For the visual assessment recordings were run at "paper speed" of 0.5 mm/sec and graded from 0 (mostly discontinuous) to 2 (mostly continuous). Then EEG recordings were run through the software for the retrieval of interburst intervals and maximum amplitudes of delta, theta, alpha and beta frequencies for each 4 sec interval. Periods of artifacts were visually assessed in the EEG and aEEG tracings and not included in the analysis. Finally aEEG parameters were correlated with EEG parameters.

T-test and ANOVA were used to compare continuous variables within various groups. Pearson coefficient correlations were calculated for linear correlation between continuous variables.

Results
Included in this report are a total of 151 tracings originating from 54 infants. 12 were recorded between 25 and 27 completed weeks of gestation, 26 between 28 and 30 completed weeks, 60 between 31 and 33 completed weeks, 43 between 34 and 36 completed weeks and 10 between 37 and 39 completed weeks. The following statistically significant correlations were found between the following parameters:
Visual assessment of EEG continuity had good correlation with the lower border voltage of aEEG (grade 0 – 4.71 micV±2, grade 1 – 6 micV±2 and grade 2 – 7 micV±2.3, P<0.001 between grades).

Visual assessment of EEG continuity vs average amplitude of aEEG (grade 0 – 4.71 micV±2, grade 1 – 6 micV±2 and grade 2 – 7 micV±2.3, P=0.004 between grades 0 and 2, P=0.003 between grades 1 and 2, P=0.621 between grade 0 and 1).

MinCFM, MaxCFM, AvCFM and AmpCFM were positively correlated with the average maximal delta activity per 10 minutes intervals (Pearson coefficient: 0.13, 0.36, 0.36, 0.35 respectively, P<0.001), average maximal theta activity (Pearson coefficient: 0.1, P=0.007, 0.22, 0.22, 0.2 respectively, P<0.001), average maximal alpha activity (Pearson coefficient: 0.12, 0.47, 0.45, 0.47 respectively, P<0.001) and average maximal beta activity (Pearson coefficient: 0.21, 0.4, 0.4, 0.36 respectively, P<0.001).

Discussion
In this preliminary report a good correlation was found between visual assessment of EEG continuity and the voltage of the lower border of the aEEG which is an index of continuity used in aEEG classification.
The different parameters of aEEG were found to be positively correlated with the average maximal activity of the different frequencies of the EEG, with the strongest correlation in the alpha and beta bands.

This report shows a good correlation between different parameters of aEEG and EEG background activities. Of note is the 5 micV line of the aEEG used to differentiate continuous with discontinuous tracings it also differentiated the EEG 0 grading for continuity from the 1 and 2 grading. In view of the algorithm of the aEEG that filters frequencies below 2 and over 15 Hetz it is surprising to see that Alpha and Beta frequencies have a stronger correlation with aEEG MaxCFM, AvCFM and AmpCFM parameters then Delta and Theta activities, a finding that we are unable to explain. In this preliminary report we did not differentiate between ill and healthy neonates and did not take into account their brain US findings or their long term outcome. We believe that taking these parameters into account will further enhance the correlations that we present. This validation of parameters of aEEG versus EEG strengthens the validity of this method as bedside monitoring of the neonatal brain preterm infants.
Benign neonatal convulsions is a rare autosomal inherited epilepsy characterized by generalized or multifocal, tonic-clonic convulsions. Symptoms occur within the first days of life and disappear spontaneously after weeks to months.

Mutations in the genes KCNQ2 and KCNQ3 have been shown to cause benign familial neonatal convulsions and benign familial infantile convulsions. Here we describe a patient with protracted neonatal seizures that were difficult to control despite several antiepileptic drugs.

The patient was born at term by normal vaginal delivery after an uneventful pregnancy. He had unilateral seizures on day 2 which were treated with phenobarbital. Despite of the treatment, unilateral seizures and later generalized seizures of short duration recurred up to 5 times/day. Brain ultrasound and MRI were normal. The patient was initiated on nitrazepam and transferred to our hospital on day 6.

On day 11 frequent subclinical seizures lasting for about 30 seconds were detected on aEEG, followed by generalized clinical seizures. EEG showed continuous activity with bilateral centrotemporal sharp waves, more pronounced on the right side. aEEG recording revealed normal interictal continuous background pattern but obvious epileptic discharge at the time of clinical seizures. Seizure control was achieved 12 days later on combination therapy with valproate, clonazepam and phenytoin. Repeated MRI was normal, extensive metabolic work-up showed no abnormalities. Karyotype was normal.

At the follow-up examination at 11 months, his neuromotor development was normal.

Mutation in KCNQ2 gene was detected which confirmed the diagnosis of benign neonatal seizures.

aEEG has proven to be useful for seizure detection and for the evaluation of antiepileptic treatment. Also normal interictal recording has been important in predicting the normal outcome and discerning from other epileptic syndromes (early myoclonic encephalopathy).
Cerebral Oxygenation and Ipsilateral Venous Flow Velocity in Critically Ill Premature Infants

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Impaired terminal vein (TV) drainage with venous ischemia is invoked in the development of periventricular hemorrhagic infarction (PVHI) in the premature infant with intraventricular hemorrhage (IVH). In vivo confirmation of this mechanism has been impeded by the inability to measure simultaneous TV flow and ipsilateral cerebral oxygenation. Our objective was to define normal TV flow velocity (TVFV) for gestational (GA) and postnatal age (PNA), and to determine the relationship between TVFV and ipsilateral cerebral oxygenation, in the preterm infant.

Methods: We studied prospectively premature infants with normal cranial US over the first 5 days of life using Doppler US (7MHz Acuson Sequoia 512, Mountainview CA) to measure TVFV and near infrared spectroscopy (NIRO-300; Hamamatsu Photonics, Hamamatsu City, Japan) to measure the ipsilateral tissue oxygenation index (TOI).

Results: We enrolled 15 premature infants with median GA of 26 weeks (range 24-29 weeks) and median birth weight of 775 grams (range 460-1460 grams). Mean TVFV (cm/s ± SE) increased significantly with PNA over days 1-4 (3.7 ± 0.3; 4.1 ± 0.4; 5.3 ± 0.4; and 6 ± 0.4 respectively; p=0.003), but not with GA. A significant correlation (p=0.007, r=0.35) was noted between TVFV and ipsilateral TOI.

Implications: TVFV shows maturational increase with postnatal age that is correlated with ipsilateral cerebral oxygenation. These preliminary findings begin to provide normative data for TVFV and its association with oxygenation of the immature brain. Further studies are needed to delineate the relationship between IVH, ipsilateral TVFV, TOI, and the development of PVHI.
Monitoring of NIRS-determined Fractional Cerebral Oxygenation (rScO2) in Preterm Infants: Comparing Left and Right Side

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Background:
NIRS measured rScO2 can be used to estimate changes in tissue cerebral oxygenation of the immature brain in the clinical setting. Because absolute values are provided it is less dependent on movement artefacts and comparisons over time are possible.

Objective:
To compare simultaneously NIRS-determined rScO2 values measured on the left (Le) and right (Ri) fronto-parietal part of the head in preterm infants on the first day of life.

Design / Methods
In 13 preterm infants (GA 29.7 ±1.4 wks, birth weight 1334 ± 258 g), rScO2 (INVOS 4100) and arterial saturation (SaO2) were monitored and stored for offline analysis. rScO2 was monitored on Le and Ri fronto-parietal part of the head during 168 ± 98 minutes. All data were averaged over 1 minute.

Results
The mean rScO2 was Le 69.2 ±8.3 %, Ri 68.8 ±8.5 %. There was a close correlation between Le and Ri measurements: r=0.85 (p<0.01). Differences between Le and Ri had a normal distribution (mean1.2 ±4.7 %). Most periods with a transient difference between Le/Ri measurements > 1SD were shortlived. 25 periods were lasting more than 5 minutes (13±6.0 minutes) and were mostly related to hyperoxia (SaO2>98%; n=4), hypoxia (SaO2<85%; n=8) and a combination of hypoxia and hyperoxia (n=6). Fig 1 shows the limits of agreement (Bland-Altman) using all data (a) and after extraction of the hypo/hyperoxic periods (b): limits of agreement: -7.0 – 10.0 % and -6.6 - 6.3 % respectively.

Conclusion:
NIRS seems to be a reliable monitoring method to assess cerebral oxygenation for a prolonged period of time, regardless of probe placement on the right or left side of the head. It must be noted that during hypoxic/hyperoxic periods measurements between Le-Ri could be transiently differ.
Pyridoxal Phosphate Responsive Patient Evaluated by Prolonged aEEG Monitoring: A Case Report

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Pyridoxal Phosphate (PP) responsive seizures are a very rare occurrence. One of the diagnostic criteria leading to genetic explorations is efficacy of the active form of vitamin B6 on refractory neonatal seizures. To evaluate PP efficiency, continuous and prolonged EEG recordings are needed. Accuracy of aEEG method needed to be evaluated in this pathology.

We report one patient who presented refractory neonatal epilepsy responsive to pyridoxal phosphate. He was the second son of healthy and non consanguineous parents. The patient experienced seizures two hours after being born. An aEEG recording was immediately performed showing numerous seizures (more than 15 per hour) and suppression burst pattern. Raw EEG confirmed suppression burst pattern and multifocal convulsions. The aEEG recording permitted to assess different anti-epileptic drugs tested during the three first weeks of his life (phenobarbitone, phenytoin benzodiazepin, pyridoxin increasing doses, vigabatrin, topiramate and finally pyridoxal phosphate progressive doses). The efficacy of PP was proven on 3 days with a progressive decrease in seizures and an improved continuous interictal trace. The patient was recorded with aEEG during a three week period without cutaneous or technical difficulty.

The main interests of the aEEG were in this case the possibility of long recording and its availability which permitted to adapt rapidly anti-epileptic therapeutics. aEEG is a very appropriate tool to diagnose pyridoxal phosphate responsive epilepsy.
Effect of Infant Massage on Amplitude Integrated Electroencephalogram (aEEG) Patterns in the Very Low Birth Weight (VLBW) Preterm Infant

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Background: Preliminary studies suggest that massage therapy may have positive impact on outcomes of premature neonates.\textsuperscript{[1-3]} The effect of massage on brain maturation as evidenced by aEEG pattern has not been evaluated.

Methods: A prospective randomized clinical trial evaluating the effects of infant massage on 60 VLBW preterm neonates (< 1500g) was performed at our institution between August 2003 and the end of March 2007. Infants were randomized either to receive massage therapy or no intervention (control). A subset of this population was evaluated by aEEG performed at 34 wks post menstrual age. aEEGs were evaluated by a blinded neonatologist (AM) and scored by a previously reported scoring system for the evaluation of brain maturation in neonates.\textsuperscript{[4]} An overall score is assigned to each infant that includes scores for continuity (Co), Cycling (Cy), amplitude of lower border (LB), and bandwidth (B). Differences between the intervention group (Grp 1) and control group (Grp 2) were evaluated by the Student’s T test for continuous variables and Chi Square for categorical variables. The Mann Whitney U test was also used to evaluate differences in median aEEG scores between the two groups.

Results: Thirteen infants were included in each group. There were no differences between the 2 groups in birth weight (BW), gestational age (GA), gender or incidence of chronic lung disease (CLD), sepsis, necrotizing enterocolitis (NEC) or intraventricular hemorrhage (IVH) (p>0.05). Three patients (23%) in Grp 2 had a somewhat discontinuous aEEG (score Co=1) whereas all patients in Grp 1 had continuous aEEG (score Co=2). Five patients (38.5%) had a less than expected total maturation score (<10) at 34 wks in Grp 2 compared to 2 patients (15.4%) in Grp 1. Median score for each domain as well as total score was not different between the two groups (p>0.05).

Implications: Benefits of infant massage on preterm infants may include improved brain maturation as evidenced by aEEG. Larger studies are needed to evaluate if these differences are statistically significant.
References:


Comparison Between 1-Channel and Multiple-Channel Cerebral Function Monitor for Detecting Neonatal Seizures

George Vartzelis MD, MRCPCH; Tonya Phillips MD; Katherine Holland MD, PhD; Donald Gilbert MD; Jason Buroker

Statement of the problem
Seizures occur commonly in infants who are treated in the Intensive Care Unit and a significant proportion of these are silent, non-convulsive seizures, especially after the first administration of anticonvulsive medication. (1, 2) Although the conventional 1-channel configuration of the Cerebral Function Monitor (CFM) is a useful tool for detecting seizures in infants, a percentage of focal seizures can be missed (3). We hypothesized that multiple-channel configurations of CFM may prove more sensitive in identifying seizures compared to the 1-channel configuration.

Statement of program, activities or methods
The EEG–CFM recordings of 49 infants (<3 months of age) referred to the Department of Pediatric Neurophysiology in Cincinnati Children's Hospital Medical Center (CCHMC) were analyzed retrospectively with emphasis to the identification of electrographic seizures. The recordings were obtained using the Nicolet/Nicolet One system which records conventional EEG data with the ability to produce CFM data by means of post-collection processing. The EEG and CFM recordings were analyzed independently by two Pediatric Neurologists and one Fellow in Electrophysiology. Each investigator analyzed separately the different modalities (conventional EEG, conventional 1-channel CFM and 4 montages of multiple-channel CFM) for each patient, noting the presence of seizures and background abnormalities. All demographic information was removed from the processed files and the investigators interpreted the recordings randomly in an attempt to minimize systematic error by comparison of the different modalities.

Summary of results or effects
The conventional one-channel CFM configuration was found to be the most accurate for detecting seizures for all three readers. The reduced accuracy of the alternative CFM modalities was primarily related to an increase in the false positive rate of seizure identification.

Implications
The alternative CFM modalities, tested in our study, were proved to be inferior to the conventional CFM configuration. Further research should be conducted to improve the diagnostic potential of the current testing modalities.
Institution where research or project was performed
Cincinnati Children's Hospital Medical Center (CCHMC), Cincinnati, Ohio, US

Bibliographic references
Amplitude-Integrated EEG Features as the Basis for Automated Background Classification

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\textbf{Background & Aim}: Amplitude-integrated EEG (aEEG) is widely used for the assessment of brain function of infants. One of the most frequently used classification (Hellström-Westas, Rosén, de Vries and Greisen, NeoReviews 2006; \textsuperscript{7}c76-c86) is based on recognition of continuous normal voltage (CNV), discontinuous normal voltage (DNV), burst suppression (BS); low voltage (LV), and flat traces (FT). The aim of the study was to analyse properties of aEEG necessary to create an algorithm for the automated classification of background states.

\textbf{Methods}: 60 EEG recordings from term and preterm infants totalling 10110 minutes were flagged on a per minute basis by the pool of raters. The distribution of margins and rank asymmetry in aEEG epochs for different background states was studied.

\textbf{Results}: Most distinctive feature of BS is positive asymmetry of aEEG voltage distribution in a sample. Values of upper and lower margins can be used to distinguish BS from FT and DNV. CNV is distinguished from all others by the value of lower margin. DNV, LV and FT are possible to separate by values of upper margin. The algorithm based on these features produced percentage of overall agreement with raters' flaggings at 94\% of theoretically possible.

\textbf{Conclusions}: The project at this stage is a promising step toward a more objective background classification method and improved assessment of the neonatal brain function.
A Randomized Controlled Trial on the Combined Use of Vitamin C and Ibuprofen in the Treatment of Infants With Hypoxic Ischemic Encephalopathy

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Background: Free oxygen radicals and pro-inflammatory cytokines are important causes for brain injury in neonates with hypoxic ischemic encephalopathy (HIE). Vitamin C when administered systemically in animals, was protective against free radicals-induced neurotoxicity (1) and intraventricular administration was protective from hypoxic-ischemic injury(2) Ibuprofen, a non-steroidal anti-inflammatory drug that, as shown by animal studies, could be neuroprotective through modulation of leukocyte activity, reducing cytokine production, inhibition of free radicals and signaling transduction (3). The efficacy of these 2 drugs in protecting the human brain in HIE has not been studied.

Aim: To test the hypothesis that a combination of anti-oxidants (Vitamin C) and anti-inflammatory (Ibuprofen) agents can ameliorate the brain injury in HIE when given immediately after birth.

Methods: Sixty asphyxiated infants admitted at Bab El-Shariya University Hospital, Cairo, Egypt, were randomly assigned to one of two groups. Group A (n = 30); infants received intravenous Vitamin C (100 mg/kg/day, 3 days) and oral Ibuprofen (Day 1: 10 mg/kg, Day 2 & 3: 5 mg/kg), and Group B (n = 30), infants received similar volume of placebo. Treatment drugs were administered within 2 hours after birth. A panel of cytokines were measured at enrollment. Neurological evaluations of all infants were done on admission, discharge and at 6 months of age. In addition, HIE was graded on admission using Sarnat and Sarnat grading and 6 months developmental screening was done using Denver Developmental Screening Test II (DDST II). This study was approved by the University IRB.

Results: There was no difference between Group A and B in HIE grading, serum IL-1β and IL-6 levels. No difference between Group A and B was noted in mortality rate (37% vs. 33%), rate of abnormal neurological exam (47% vs. 55%) and rate of delayed scores on DDST II at 6 months (32% vs. 40%). Serum IL-1β and IL-6 levels were higher in asphyxiated infants when compared to controls (P < 0.001) and their levels correlated with the severity of illness (P<0.01). Elevated Serum IL-6, but not IL-1β, correlated with poor neurodevelopmental outcome at 6 months (P<0.001).
**Implications:** Although oxidative stress and inflammatory cytokines are increased in HIE, the early administration of vitamin C and Ibuprofen did not seem to reduce mortality or improve neurodevelopmental outcomes measured at 6 months of age. It is not clear whether our protocol was not effective in blocking free radicals and inflammatory cytokines or whether other mediators have stronger role in brain damage in infants with HIE.

**References:**
The Utility of Amplitude Integrated Electroencephalograph During Neonatal Cardiac Surgery

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Background
Neonates undergoing surgery with cardiopulmonary bypass are cooled as a neuroprotective mechanism. The extent of hypothermia is thought to influence the degree to which cerebral metabolic activity is reduced in order to minimise potential ischaemic injury. Methods of monitoring cerebral function during this high-risk period are limited.

Aims
It is the aim of the current study to use two-channel amplitude integrated electroencephalography (aEEG) to monitor cerebral function intra-operatively in a cohort of newborn infants with either transposition of the great arteries (TGA) or hypoplastic left heart syndrome (HLHS). Those with TGA were cooled to 32°C whilst those with HLHS were cooled to 21°C to 25°C and underwent regional cerebral perfusion during bypass. The two groups were then compared and short term outcomes studied.

Methods
Newborn infants undergoing cardiac surgery at The Royal Children’s Hospital in Melbourne with either HLHS or TGA were included in the study. Infants underwent cerebral magnetic resonance imaging pre- and post-operatively. Pre-, intra- and post-operative aEEG (TM BRM2, BrainZ Instruments) were recorded. Findings from the period extending from 20 minutes prior to cardiopulmonary bypass until 20 minutes following cessation of bypass are reported here. Minimum and maximum amplitude for each hemisphere were correlated with oesophageal temperature.

Results
From November 2005 until July 2007, 10 infants with HLHS and 10 with TGA have been studied. All were full-term with a mean birth weight of 3.4kg (±0.6). Median age at surgery was 9 days (range 7-15) in the TGA group and 2 days (1-7) in the HLHS group. In the TGA group there were no significant differences in the aEEG parameters between normothermia and mild hypothermia on cooling to 32°C. One infant with pre-operative brain injury had an asymmetric background trace. In the HLHS group the change in minimum and maximum amplitude correlated with cooling to 21-25°C. Five infants had isoelectric traces bilaterally throughout the period of moderate hypothermia. Of the five who continued to display electrical activity on at least one hemisphere despite a nadir of
hypothermia, four subsequently died prior to discharge from hospital and one developed extension of pre-operative haemorrhagic infarcts.

**Conclusion**
Mild hypothermia is not associated with depression of cerebral electrical activity. Cooling to, and rewarming from, moderate hypothermia is associated with concomitant changes in aEEG amplitude, but is inconsistently associated with persistence of the isoelectric state at the nadir of hypothermia. Despite the small numbers studied, we observed significantly worse short-term outcome in infants who had increased cerebral activity during this period.
Automated Neonatal Seizure Detection
Correlation of Initial EEG Background Activity with Seizures, Mortality and MRI Findings in Infants with Moderate-Severe Encephalopathy Treated with Whole-Body Hypothermia

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Objective: Does initial EEG background activity predict seizures, mortality, and MRI evidence of injury?

Methods: Whole-body hypothermia was performed in 30 infants gestation ≥ 36wks within <6hrs of age who met criteria for moderate-severe neonatal encephalopathy [Shankaran, et al 2005]. Continuous video-EEG monitoring (neonatal montage) was reviewed by a board-eligible pediatric epileptologist and a boarded pediatric epileptologist for background activity in the first 24 hours of life and seizures. Background ratings were based on modifications of previous ratings scales [Laroia, et al 1998, Tharp, 1997], to include varying degrees of discontinuity. MR imaging was performed on DOL#6-12.

Results: 26 records were available for review. No infants had normal (NI) background activity. Background (Bkgnd) activity could not be evaluated in 2 infants who had continuous seizures. Both had global injury on MRI and one had severe PPHN resulting in withdrawal of support.

Mild through mild-moderate background abnormalities were seen in 12 infants. None had seizures. Only 2 infants with mild through moderate background abnormalities had support withdrawn. Both were on ECMO, one of whom had postnatally diagnosed congenital heart disease. Infants with mild through moderate background abnormalities who survived had cortical or subcortical white matter injury on MRI.

Infants with moderate-severe background abnormalities (7) had either cortical or subcortical white matter injury or combined cortical and deep grey nuclear injury on MRI. Three had seizures. All survived. Five infants had severe background abnormalities (all isoelectric). Two had seizures. One had combined cortical and deep grey matter injury. The other had support withdrawn due to severe PPHN and therefore neuroimaging was unable to be performed. The 3 without seizures showed herniation on CT scan of the head with global injury on MRI and 2 had support withdrawn.

Only infants with moderate-severe or severe background abnormalities had seizures.
A total of 6 patients had support withdrawn. Background abnormalities and presence of seizures were variable in this group. The 2 infants with seizures had status epilepticus with only electrographic seizures and these were the only two infants in our group of 26 infants with exclusively electrographic seizures. 5/6 infants who had support withdrawn either had PPHN (3/4) or were on ECMO (2/4).

**Conclusion:** Consistent with previous studies of infants with encephalopathy, the EEG background correlates well with seizures and MRI patterns of injury. Larger cohorts with long term developmental follow-up are needed to determine if the EEG background features also predict developmental outcomes.
aEEG in Birth Asphyxia: An Accurate Tool for Prognosis? A French NICU Center’s Two Year Experience

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Objective: To determine whether two / four channel continuous electroencephalography applied within six hours of birth is a reliable method to predict neurological outcome following birth asphyxia.

Method: A continuous two or four channel EEG was performed within 6 h of birth in 25 infants who suffered birth asphyxia. aEEG recordings were defined in three groups: normal - group 1, moderately depressed - group 2 and severely depressed - group 3. Standard EEG, cerebral MRI and neurological outcome assessed between 9 to 38 months of age were compared to aEEG assessments.

Results: aEEG recording were commenced less than 3 hours after birth in all cases immediately after NICU admission or after birth. Every baby either had technically satisfactory recordings or were excluded of the study. Every baby had a standard EEG as soon as possible in range of 3 to 60 hours and every baby but one had an MRI within 10 days (mean time 7 days). Nineteen (76 %) of babies were admitted in NICU unit either after 6 pm or on the week-end. aEEG recordings had a mean duration of 48 hours and interpretations were made at 6, 24 and 48 hours. It is the 6 hours recording which is take in count for the groups. Evolution of the tracing, modulation (sleep/waves cycling) and presence of seizures were studied for each one.

For the group 1 (10 babies had a normal aEEG), standard EEG and MRI were normal or subnormal respectively in all cases and 9 cases. All babies but one had a normal neurological outcome. Concerning group 2 (11 cases) standard EEG was abnormal in all cases and slow continuous, discontinuous with physiological pattern (discontinuous type A) or without physiological pattern (discontinuous type B). MRI was abnormal in 7 cases. Five children have a normal outcome and 6 have neurological disabilities. aEEG criteria for favourable outcome were improvement of the tracing within 48 hours and or sleep/wake cycling and or a discontinuous type A raw EEG. In group 3, eight patients had a severely depressed aEEG. Standard EEG was either inactive or burst-suppression in 7 cases and discontinuous type A (EEG recording delayed from 36 hours in one case). MRI was abnormal in all cases but one. Outcome was death (2) or severe handicap (5). The normal neurological evolution patient had an improvement within 48 hours of his aEEG (severely to moderate depressed with sleep/wake cycling appearance at this time). All infants with severely depressed aEEG at 24 and 48 hours died or developed neurological abnormalities. All these infants had an abnormal EEG.
**Conclusion:** All infants who had a normal neurological outcome had a normal aEEG with presence of sleep/wakes cycling at 6 hours of life. In other groups, patients whose aEEG improved within 48 hours had a good outcome. aEEG is an accurate tool for assessing the severity of birth asphyxia soon after insult in association with standard EEG. Its availability is every time an essential advantage for NICU.
Two Years Assessment of Amplitude-Integrated Electroencephalography to Define Normal Criteria for the Preterm

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Purpose
Term and preterm newborn care requires electrophysiologic investigations for seizure detection and therapeutic management or prognosis purposes. Amplitude-integrated electroencephalography (aEEG) offers an accessible by non expert, bedside continuous cerebral monitoring. Two years utilization of aEEG in a neonatal intensive care unit provided data for preterm babies leading to define normal criteria depending of post-conceptional age.

Methods
240 preterm babies received prospectively a continuous cerebral monitoring coupled with standard EEG and neuro-imaging (US and/or MRI) during two years (January 2004 to December 2005). Normal neurological outcome babies were defined by normal raw EEG, neurological imaging and neurological outcome at 2-3 years (Denver developmental screening test). AEEG analyzed data were: lower, upper borders amplitude, bandwidth, cycling, discontinuity duration. Technically unsatisfactory aEEG recordings were excluded.

Results
One hundred preterm babies were enrolled: 41 patients delivered at 24-27 gestation weeks (GW) and 59, 28-32 GW. aEEG were performed 4,47 days after birth mean. Five percent of the population received sedative drugs during recording. 78 % of babies less than 28 weeks old had a lower border amplitude inferior to 5 microvolts, 47 % for the older group. The bandwidth decreased with maturation: 25 mm for the babies less than 28 weeks gestation and 20 mm for the older group. Cycling was respectively present in 53 % and 66 % of the aEEG. For these immature babies, transient rise in the background activity (saw-tooth) reliable to seizures in term babies are frequent (29% and 13 % respectively for the two groups) and don’t correspond to convulsive activity.

Conclusion
aEEG is an accurate tool for assessing the neurological outcome of preterm. Normal criteria aEEG depending of gestational age, essential for prematurity prognosis are defined. Its availability every time is an essential advantage for NICU especially for vulnerable preterm infants.
EEG and Clinical Characteristics of Post-Asphyxial Neonatal Seizures

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Aim: To describe the EEG and clinical characteristics of post-asphyxial neonatal seizures.

Methods: Review of 24-72 hour long video-EEG polygraphy recordings (done within 24 hours of birth) and patient charts in 83 consecutive neonates with moderate to severe birth asphyxia. In 26/34 patients with recorded seizures, detailed classification of EEG localisation, duration, frequency, amplitude and spread of 609 seizures was done (median 17 per patient, range 2-90).

Results: Seizures were recorded in 34/83 (39 females) neonates. 23 of them had clinical seizures before start of EEG monitoring. However, only 5 had clinical seizures recorded with EEG correlate. Electrographic seizures started after a mean of 22.7 hours postpartum (range 8-48), continuing for 4-38 hours after start of monitoring (mean 21.5). Ictal discharges consisted of sinusoidal waves or runs of rhythmic sharp waves or a mixture of these patterns, predominantly at a frequency of 1.5 Hz (range 0.5-7). Though seizures involving all scalp regions were recorded, majority (53%) of the seizures were localised to the central regions. Most of the seizures with a frequency of ≥3 Hz had temporal region involvement. Neonates with recorded seizures had a poorer outcome (death or severe motor handicap in 24/34 vs 21/49, p = 0.013), as well as a severely abnormal background EEG activity (consistently <5 µV in 22/34 vs 20/49, p = 0.032). However, newborns with severely abnormal background EEG activity in both groups had a poor outcome (seizure group 19/24 vs non-seizure group 20/21, p = 0.114). There was no difference in the number of patients with severe abnormalities on brain MRI between the seizure and non-seizure groups (20/34 vs 21/49, p = 0.152).
**Conclusions:** Majority of post-asphyxial neonatal seizures show electro-clinical dissociation. Though most neonates with recorded seizures have a poor outcome, this seems to be associated with a severely abnormal background EEG activity rather than the occurrence of seizures themselves. Electrographic characteristics like seizure discharge frequency seem to be determined by seizure location. Preponderance of seizure foci in the central regions underscores the importance of including these channels in the EEG trends used for long-term monitoring in asphyxiated neonates.
Effects of Opioids on Cerebral Oxygenation (rScO₂), Fractional Tissue Oxygen Extraction (FTOE) and Amplitude Integrated Electroencephalography (aEEG) in Preterm Infants Treated with InSurE procedure

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Background: Opioids are widely used as analgetic and sedative drugs in preterms for invasive procedures. The effects of opioids on regional cerebral oxygenation, oxygen extraction and aEEG are not exactly known.

Objective: The effects of bolus administered opioids in preterm infants treated with Continuous Positive Airway Pressure (CPAP) and the InSurE procedure (Intubation, Surfactant, Extubation) on cerebral oxygenation (rScO₂) and oxygen extraction (FTOE) using near infrared spectroscopy (NIRS) and aEEG were evaluated.

Methods: Twelve infants (gestational age 29.1 ± 1.3 weeks, birth weight 1206 ± 349 grams, postnatal age 19 ± 11 hours) treated with CPAP and InSurE were monitored for blood pressure (MABP), arterial saturation (SaO₂), rScO₂, FTOE (SaO₂-rScO₂/SaO₂) and aEEG. From these parameters ten minutes periods were selected and averaged at 120 and 20 minutes before and at 30 minutes, 1, 2, 6, 12, 24 hours after the administration of opioids. aEEG was analysed by qualitative (Burdjalove score) and quantitative (mean electrical cortical activity (µV/10min)) method. Burdjalov scores were determined blinded by an independent person at 2 hours before and 1, 6, 12 and 24 hours after the opioid bolus. Each patient was matched for GA, birth weight and postnatal age with infants treated with CPAP without opioids.

Results: MABP and SaO₂ were not different between groups. rScO₂ and FTOE were comparable between groups except at 30 minutes after opioid administration. Quantitative aEEG however was significant lower in the InSurE infants after opioids up to 12 hours compared to controls. Also during this period of time Burdjalov scores were significant lower after opioid administration in the InSurE group compared to controls.

Conclusion: Bolus administered opioids in preterms treated with InSurE have no influence on rScO₂ and FTOE. However opioids decreases aEEG for a prolonged period of time.
Thermal Transfer and Gradients in Neonatal Hypothermia Treatment

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and Pediatrix Medical Group

Background: Hypothermia treatment is an effective treatment for moderate to severe neonatal hypoxic-ischemic encephalopathy. Two treatment approaches have been used. Both treatments include a targeted reduction in patient core temperature. Treatment has been administered using: 1) different methods to accomplish cooling, and 2) differing target core temperatures. A thermodynamic analysis was done of these treatment methods.

Methods: Hypothermia treatment was analyzed using standard physics concepts and formulas of thermal transfer. The primary mode of external thermal transfer during therapeutic hypothermia is conductive. Calculations were done using known, measured and estimated quantities of temperatures, surface areas, and thermal coefficients including tissue. These observations were combined with existing data concerning internal thermal distribution in hypothermia therapy. For the purposes of this analysis, we ignored variables believed to be small, nonquantifiable or nonmodifiable; including tissue thermogenesis, vasoactive responses, insulation such as fat, inhomogeneity, respiratory thermal exchange, and environmental convective and radiant contributions. Results, and clinical implications, of thermodynamic transfer are presented.

Results and Analysis:

External Cooling Therapy Conductive thermal transfer is governed by Fourier’s Law of Heat Conduction, expressed in the linear case:

\[ Q = - \frac{K A \Delta T}{S} \]

where:
- \( Q \) = heat transferred per unit time (Watt = joule/sec)
- \( K \) = thermal conductivity of the material (W/m °K)
- \( A \) = heat transfer area (m²)
- \( S \) = material thickness (m)
- \( \Delta T \) = temperature difference, or gradient, across the material (°K)

Signage reflects the direction of heat transfer; Negative is heat removal, or cooling

Conductive Area Whole body cooling is administered using a thermal cooling blanket underneath the supine baby. Contact area depends upon the size of the baby and the exact contact points. Maximal contact and conduction, occurs at the posterior pressure points (cranium, back, buttocks, and legs) since the thermal conductivity of air, at noncontact points, is poor. Using these observations, with a typical patient weight of 3.5kg, the effective area of thermal transfer is estimated at
approximately 40 x 16 cm, or 640 cm² (0.064 m²). Head cooling is administered with a cap placed in direct contact with the baby’s cranium. Contact area depends on the cap size, selected as appropriate for the patient size. There are both direct contact portions and open vents in the cap. Measurement of the medium size cap reveals an estimated effective area of thermal transfer area of about 250 cm² (0.025 m²). Thus, the effective area of conductive thermal transfer area in whole body cooling is about two and a half times that of head cooling:

**Heat Transfer Area** \( A_{BC} = 2.56 A_{HC} \)
where BC is body cooling and HC is head cooling

**Core Cooling** Both methods are “systemic” hypothermia, with a specific target core temperature. The whole body and head cooling methods both cool to a deep core body temperature, measured by esophageal or rectal probe respectively. The target temperature differs (by current convention) - 33.5°C in body hypothermia, and 34.5°C in head cooling. Optimal core temperature for treatment is unknown. If we assume a baseline infant temperature of 36.5°C, then this represents either a 3.0°C or 2.0 °C reduction from that baseline. Thus, the total thermal transfer in whole body cooling is about 1.5 times that of the head cooling technique:

**Heat Transfer/Time** \( Q_{BC} = 1.5 Q_{HC} \)

**Tissue Conductivity** The thermal conductivity of most tissues has been measured to be somewhat higher than that of water (0.6). Solid tissue is higher (more conductive), and lung is lower (more like that of air). The tissues of transfer between source and core include muscle (5.5), brain (1.7), blood (1.6), and major organs such as liver (3.3) \(^4\). Let us assume an average of \( K = 3 \) for both methods. Let us also assume an arbitrary 5cm from source to core (baby ‘thickness’ \( S \)), for both methods.

**Internal Blood Flow Convection** Internal thermal distribution is accelerated by the convective transfer of rapid blood circulation, especially in highly vascular areas such as the brain \(^5\). While this may reduce internal gradients, they still clearly exist. It has been shown that there are significant thermal gradient distributions from external source to core, using both direct invasive thermometry in animals \(^6,7\), and by various models \(^8,9,10,11\) in humans.

**External to Core Thermal Gradients** The applied temperature, on the baby’s surface, drops significantly below the target core temperature. This physically must be the case to actively cool a warm baby – a gradient must be created. The blanket or cap surface temperature is often quite cold, but has seldom been systematically reported. The device manufacturer usually has some lower operational limit. In selective head cooling, this gradient variance produces very cold regions (as low as < 27-30°C) which may include hair, skin, scalp fat, skull, dura, and at least the superficial 2 cm of brain \(^6\).

**Gradients and Time** \( Q \) is heat transfer/time; energy expressed in Watts. The variable embedded within \( Q \) is time. If the temperature gradient \( dT \) is smaller, then...
Q is lower and the thermal change must take longer - in order to achieve a given total transfer. The dynamics of thermal transfer during the rapid cool down phase are robust, with maximal gradient, and Q. This transfer is reversed, and more gradual, during warm up. There is a smaller but ongoing bidirectional transfer during hypothermia maintenance. Occasional overhead radiant warmer use would create a second opposing gradient.

**Comparative Gradients** Let us examine cooling with both techniques. Since starting temperatures are similar in babies prior to treatment, the temperature gradient \( dT \) implies the temperature which must be applied at the surface (skin) in order to achieve the target core temperature. Heat transfer is calculated, using the areas A, tissue coefficient S, and total heat transfer estimates Q above, and solving for comparative \( dT \).

\[
Q_{BC} = K_{AB} \frac{dT_{BC}}{S} = 1.5 \frac{Q_{HC}}{S} = 1.5 \left( K_{AH} \frac{dT_{HC}}{S} \right)
\]

Substituting and calculating; see Appendix for math calculations
\[
dT_{BC} = 0.586 \text{ dT}_{HC} \quad \text{or} \quad \text{dT}_{HC} = 1.71 \text{ dT}_{BC}
\]

Thus, the thermodynamic analysis shows what is obvious intuitively. A smaller surface area (at any location) requires a larger temperature gradient, and/or a longer time of cooling, in order to attain core cooling. Head cooling requires 1.7x the temperature gradient, compared to body cooling (and/or more cooling time) in order to achieve the target core temperatures – though head cooling utilizes a ‘less cool’ core target by 1°C.

**Discussion**

This thermodynamic analysis demonstrates the principles of applied temperature requirements and gradients, considering surface area, conduction and convection, and total transfer. The difference noted between methods carries important clinical implications, and raises several important questions:

- Is there a safe minimal external temperature?
- Is applied temperature, location or method related to skin adverse effects? Does positional change of contact points affect this?
- What is the optimal therapeutic brain, or core, temperature?
- Is it safer, or more effective, to induce a temperature gradient across the back, or across the cranium?
- Are two opposing gradients to achieve a target core temperature as safe as single gradient servo control?
- If the aim of cranial cooling is to achieve even core cooling; is it really logical or necessary to apply this cooling only to the cranium?
• Is temperature variance within the brain, including 'supercooled' superficial deep cortex/white matter, of concern? How might gradients impact brain injury in either superficial or deep structural areas?

• Should we consider entirely different methods to achieve effective and safe cooling therapy? For example, forced air cooling (predominantly convective) could be delivered in a ‘reverse’ incubator apparatus. The dynamics would likely dictate a slower cool down, smaller gradients, and an extremely stable steady state. Such systems might be applicable to meet the need for cooling in transport.

More data is needed with both methods - regarding applied surface temperatures, skin effects, cooling times, and optimal target temperature. Internal brain and body temperatures, thermal gradients, and their potential effects must be better understood as these therapies evolve.

**Appendix: Calculations**

\[
Q_{BC} = \frac{K \ A_{BC} \ dT_{BC}}{S} = 3 \times 0.064 \times \frac{dT_{BC}}{0.05} = 1.5 \ Q_{HC} = 1.5 \times K \ A_{HC} \ dT_{HC} \ / \ S = 1.5 \times 3 \times 0.025 \times \frac{dT_{HC}}{0.05}, \ or
\]

\[
3 \times 0.064 \times \frac{dT_{BC}}{0.05} = 1.5 \times 3 \times 0.025 \times \frac{dT_{HC}}{0.05} \quad 0.064 \ dT_{BC} = 1.5 \times 0.025 \times dT_{HC}
\]

\[
0.064 \ dT_{BC} = 0.0375 \ dT_{HC} \quad dT_{BC} = 0.586 \ dT_{HC}
\]
Nursing Care of the Infant Treated with Neuroprotective Hypothermia

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Background: Hypothermia treatment has been shown to be effective and safe in improving outcomes after moderate to severe perinatal asphyxia \(^1,^2\). We developed and implemented a treatment program for our perinatal region in South Carolina \(^3\). We report our experience with the process of program implementation, and provide an outline of our clinical experience concerning the bedside clinical care of these babies.

Methods: We developed a treatment program between May 2005 and July 2006. These steps included: 1) evaluation of the evidence concerning hypothermia treatment, 2) selection of treatment methodology (NICHD whole body systemic cooling) based on efficacy, safety, ease of use, and cost effectiveness, 3) equipment acquisition, 4) protocol and standard order set development, and NICU staff education, led by a core multidisciplinary planning team, 5) a site visit to a treatment center \(^4,^5\), 6) regional outreach education concerning eligibility, referral and transport, 7) establishment of data reporting to the Vermont Oxford Network Encephalopathy Registry, 8) arrangement of neurodevelopmental followup, and 9) approval of this treatment as an investigational program, under the supervision of our institutional Investigational Review Committee (IRC), requiring parental informed consent. This treatment was implemented commencing August 2006. This report describes nursing care and recommendations based on our experience in treating infants with neuroprotective hypothermia.

Results, Observations and Recommendations:

Patient Eligibility and Entry Standard NICHD entry criteria \(^1\) included: infants >36wk and 1800gm, resuscitation at birth, severe acidosis, moderate or severe encephalopathy, and age < 6hrs at enrollment. Over sixteen months, we have had twelve referrals from a referral region of 25000 annual births.

Consent Process and Transport The parental consent process is challenging. The mother is immediately postpartum. Often this has been an emergent/operative delivery, and she may be at a referral facility. Consent by an unmarried father is not acceptable in our state. We used consent document transmission by facsimile, and involved the referral physician and transport staff in
assuring good communication. The consent process may delay transport and therapy initiation. Transport was done as expeditiously as possible, with passive cooling recommended.

NICU Nursing Care:

**Pre Therapy Preparation**  The thermocontroller was set up prior to admission, and the blanket precooled to 33.5°C. Precooling results in a more rapid cooldown. We used a Cincinnati SubZero (CSZ) Blanketrol III digital thermocontroller, with improved stability around the target temperature, compared to the model used in the NICHD study. An esophageal temperature probe provides servo control of the cooling unit output. The radiant warmer is turned off until full core warmup is completed after 72hr.

**Initiation**  Cooldown was generally rapid, with a median cooldown time of 35 minutes (range: 15m – 1hr 45min). Baseline and interval lab data were obtained. Frequent temperature recordings were done, from several sites, especially during cooldown and warmup. Other vital signs were done frequently as well.

**Expectations**  It was helpful for staff and parents to understand common expectations, including sinus bradycardia, cyanosis and/or mottling, skin distinctly cool to touch, and occasional shivering.

**Parental Observations**  Parents were anxious concerning the asphyxia and HIE, multisystem illness, and the intimidating nature of intensive support which might include respiratory ventilation or oscillation, pressors, nitric oxide, cooling therapy and monitoring including aEEG. Neuromuscular blockade was a distinct area of concern. The prognosis was often unclear in the early phase of treatment. Repeated information and support were essential.

**Maintenance**  over 72 hours was generally uneventful, other than the expectations cited, and complications occurring in these critically ill infants. It was important to check frequently for good coolant circulation, including inspection for hose twisting or folded blanket corners. Controller resets can be accomplished by a simple power off/on but were rarely required.

**Warmup**  was very gradual, with the thermocontroller setpoint increased by 0.5 °C q 30min, and the core temperature trailing this. We did not observe seizures during warmup.

**Skin Care**  Skin complications of several types have been reported. We instituted routine patient repositioning q2hr to change thermal contact points, and regular skin examination. One thin cotton blanket was placed between the cooling blanket and baby, for attenuation of pressure points, patient comfort and to prevent soiling. We observed no skin complications.
**Pain and Discomfort Assessment**  Our NICU does routine pain/discomfort scoring on all babies, using the PIPP 7 scale. Pain scoring systems are of limited value in these babies because the neurological indicators are altered by the encephalopathy, and the autonomic indicators are altered by the cooling treatment.

**Complications and Adverse Events**  No identifiable treatment complications occurred. Complications of the severe asphyxia/HIE included respiratory failure, cardiogenic shock, pulmonary hypertension, renal failure, hepatic failure, brain injury, and death.

**Discussion:** We felt that a thorough process of multidisciplinary preparation, education, and regional collaboration were important elements in successful treatment implementation. No eligible infants have been born in our referral region during this time period who were not treated in a timely manner. Referrals are infrequent, and often with little notice, yet each treatment startup is urgently time sensitive.

Nursing care of these infants is manageable, within the context of the complex care of these infants, based upon hypothermia protocols and education. The core resource team remains a valuable element in quality assurance. We recommend 1:1 staffing for these babies during the cooldown and warmup phases.

We identify some needs, and possible future considerations in hypothermia therapy: 1) **Transport:** effective and safe cooling in transport is urgently needed - using gelpacks 14, air cooling, or a mini-controller. Most of these eligible patients are born outside tertiary NICUs. 2) **Consent/Rapid Induction:** The data favoring early treatment is very strong 8. If the evidence for safety and efficacy of this treatment continues to be favorable 9,10,11, an individual institution may consider offering this therapy without a delaying consent process. Most experienced institutions offer this therapy without a formal investigational consent process 12. Parental consent rate is extremely high 13,14, the evidence base is strong, and time is of the essence in initiating therapy. The goal in cooling therapy should ultimately be the first “golden hour.” 3) **Buffer Blanket:** The adult heat sink blanket (‘sail’) is no longer required when using the precise CSZ Blanketrol III digital thermocontroller, according to the manufacturer 6 and experienced users 14. This cumbersome accessory can be omitted with this improved, more stable unit. 4) **Pain Assessment:** A new system of pain and discomfort assessment needs to be developed for this group of infants.

This report describes the implementation of a Hypothermia Neuroprotection program for infants with moderate to severe perinatal asphyxia. Our clinical experience regarding bedside clinical nursing care is presented.

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