Neurodevelopmental outcomes after neonatal cardiac surgery: Role of cortical isoelectric activity

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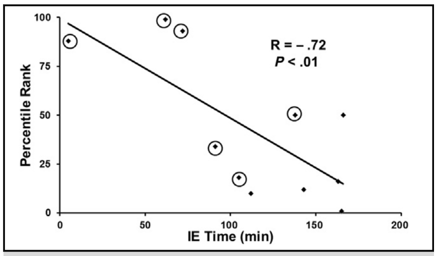
ABSTRACT

Objectives: Neonates with congenital heart disease are at risk for impaired neurodevelopment after cardiac surgery. We hypothesized that intraoperative EEG activity may provide insight into future neurodevelopmental outcomes.

Methods: Neonates requiring surgery had continuous intraoperative EEG and hemodynamic monitoring. The level of EEG suppression was classified as either: slow and continuous; moderate burst suppression; severe burst suppression; or isoelectric (no brain activity for >3 minutes). Follow-up neurodevelopmental outcomes were assessed using the Vineland Adaptive Behavior Scale II (Vineland-II).

Results: Twenty-one neonates requiring cardiac surgery developed a slow and continuous EEG pattern after general anesthesia. Ten neonates (48%) maintained continuous brain electrical activity with moderate burst suppression as the maximum level of EEG suppression. Eleven neonates (52%) developed severe burst suppression that progressed into an isoelectric state during the deep hypothermic period required for circulatory arrest. However, the duration of this state was significantly longer than circulatory arrest times (111.1 ± 50 vs 22.3 ± 17 minutes; $P < .001$). At a mean follow-up at 5.6 ± 1.0 years, compared with neonates with continuous brain electrical activity, neonates who developed an isoelectric state had lower Vineland-II scores in communication. There was an inverse relationship between composite Vineland-II scores and duration of isoelectric activity ($R = -0.75$, $P = .01$). Of neonates who experienced an isoelectric state, durations of >90 minutes were associated with the lowest Vineland-II scores (125.0 ± 2.6 vs 81.1 ± 12.7; $P < .01$).

Conclusions: The duration of cortical isoelectric states seems related to neurodevelopmental outcomes. Strategies using continuous EEG monitoring to minimize isoelectric states may be useful during complex congenital heart surgery. (J Thorac Cardiovasc Surg 2015;■:1-8)



Relationship between the duration of isoelectric activity and neurodevelopmental outcomes.

Central Message

Longer duration of an intraoperative cerebral isoelectric state, as measured by EEG, in neonates undergoing surgery for congenital heart disease, is associated with worse neurodevelopmental outcomes.

Perspective

The use of intraoperative neurologic monitoring for neonates requiring pediatric cardiac surgery has been unreliable in detecting postoperative neurodevelopmental outcomes. This study found a correlation between worse such outcomes with longer duration of an isoelectric brain state, as measured by intraoperative EEG. Thus, use of intraoperative EEG monitoring may help provide further insight into and ability to affect neurodevelopmental outcomes in this population.

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Neurodevelopmental delay is commonly diagnosed at 1 to 10 years after neonatal cardiac surgery,[1-4] and likely results from a combination of pre- and intraoperative factors.[1-8] However, despite increased awareness, the exact mechanism(s) responsible for neurodevelopmental delay remain elusive. In addition, only minimal advances have been made to improve neurodevelopmental outcomes in neonates during complex cardiac procedures.[7,8]

Although initial results of using selective antegrade regional perfusion were promising,[9] data are conflicting as to whether this approach improves outcomes, compared with deep hypothermic circulatory arrest (DHCA).[10]

Abbreviations and Acronyms

CBEA	= continuous brain electrical activity
CPB	= cardiopulmonary bypass
DHCA	= deep hypothermic circulatory arrest
EEG	= electroencephalogram
HLHS	= hypoplastic left heart syndrome
Vineland-II	= Vineland Adaptive Behavior Scale II

Furthermore, monitoring devices designed to identify and predict poor neurodevelopmental outcomes have not led to clear delineation of those at highest risk. Near-infrared spectroscopy, cerebral oximetry, and electroencephalograms (EEGs) have, in selected case reports, demonstrated benefit; however, that improvement has not been observed within a larger population.[11-14]

In recent intraoperative EEG monitoring, during the repair procedure for neonates who had congenital heart disease, we observed distinct EEG patterns that were primarily dependent on body temperature.[15] We found that an isoelectric state in the brain, defined as absence of brain activity, began before, and extended beyond, the DHCA time. Therefore, the aim of the current study was to determine the impact of an intraoperative cortical brain isoelectric state on intermediate-term neurodevelopmental outcomes.

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METHODS

Institutional review board approval and parental consent were obtained. Neonates aged <30 days who required cardiac surgery, and were previously enrolled in a prospective observational study,[15] were assessed for neurodevelopmental outcomes. Exclusion criteria included preoperative seizure activity, known central nervous system injury, and multiple extracardiac congenital anomalies. A limited central nervous system assessment was performed preoperatively by the treatment team, who assessed for gross neurologic dysfunction; a preoperative EEG, without sedation of the patient, was used to assess for seizures. Routine care at our institution did not include brain imaging prior to surgery, unless the clinical status suggested the presence of central nervous system dysfunction.

Electroencephalogram Recordings

Gold-plated EEG electrodes were affixed to the scalp, and lead placement was in accordance with the international 10-20 system with the exception of FP1 (left frontal lobe) and FP2 (right frontal lobe), as described elsewhere.[15] A baseline 30-minute preoperative EEG was obtained in all neonates 24 hours prior to surgery, with the patients awake and without sedation. The EEG recordings resumed upon arrival at the operating room and were made continuously for the duration of the procedure.

Analysis of EEG recordings was performed postprocedure by 2 of the investigators, under blind study conditions, and fluctuations in EEG activity were linked to events recorded from within the intraoperative record. The EEG activity was classified as either: (1) appropriate for age: normal for patient's age; (2) slow and continuous: EEG with slower frequencies but remaining continuous; (3) having moderate burst suppression: intervals of <30 seconds between bursts; (4) having severe burst suppression: intervals of 31 to 179 seconds between bursts; or (5) isoelectric: no brain activity for >180 seconds (Figure 1).[15] Intraoperative events were extracted from the intraoperative record according to a predetermined protocol, by a single individual, under conditions of study blinding to patients' EEG data.

Operative Technique

All neonates required cardiopulmonary bypass (CPB) for either cardiac repair or palliation. Fentanyl and pancuronium were used for anesthetic induction, and anesthesia was maintained with fentanyl and isoflurane throughout the remainder of the procedure. Arterial cannulation was aortic in all cases, except for neonates who received regional perfusion.

Regional perfusion (n = 4) was used in patients with hypoplastic left heart syndrome (HLHS) and was accomplished after the cannulation of a 3.5-mm graft sewn to the innominate artery. Next, neonates were cooled to 18 to 20°C, with flows of 20 to 30 ml/kg. In the absence of DHCA, all patients were cooled to 32 to 34°C. Cooling was achieved by lowering the blood temperature by 1°C every 1 to 2 minutes. Rewarming was initiated, typically after removal of the aortic crossclamp, and achieved via increasing the arterial blood temperature by 1°C every 3 minutes. While patients were on CPB, blood glucose was maintained between 80 and 200 g/dL (using insulin and 50% dextrose solution [D50]); PaO_2 (ratio of partial pressure arterial oxygen and fraction of inspired oxygen) was maintained at >100 mm Hg; $PaCO_2$ (partial pressure of carbon dioxide in the arterial blood) levels at 35 to 45 mm Hg; and hemoglobin >7.0 g/dL, corrected to 37°C, utilizing pH-stat cooling and alpha-stat rewarming.

Follow-up

In 2013, the parents of the 32 neonates who previously had intraoperative EEG recordings[15] were contacted and asked to participate in the assessment of their child's neurodevelopmental outcome. The Vineland Adaptive Behavior Scale, second edition (Vineland-II) was used to evaluate attainment of neurodevelopmental milestones. The Vineland-II is a reliable, well-validated omnibus measure of adaptive function that evaluates adaptive skills in multiple domains, including communication, motor function, activities of daily living, social skills, and maladaptive behaviors.[16,17] The Vineland-II, which is appropriate for use across the lifespan, was chosen because of the age of the participants, and because it allows for evaluation of multiple areas of development.[16,17]

Parents who agreed to participate in this aspect of the study were mailed the Vineland-II questionnaire and asked to complete and return it. A post-completion telephone interview was performed by 1 of the investigators, under blind conditions, who was trained in the administration of the Vineland-II and could thereby ensure the accuracy and completeness of parental responses. The questionnaires were scored using standard software[18] that generated an age-adjusted score—reflecting global performance in relation to same-age peers—and an individual score for each functional domain (communication, activities of daily living, social skills, and motor skills). In addition, z-values for the composite Vineland-II score (summarizing global adaptive skills across all areas assessed), as well as from individual domains, were determined to demonstrate the degree of neurodevelopment compared with the mean for age (z-value mean = 0; SD = 1.0).

Statistical Analysis

Descriptive statistics were used to describe the study measures, such as mean, SD, median with 95th percentiles, frequency, and percentage. Continuous variables were compared between study groups, using a Mann-Whitney U test; categoric variables were compared using Pearson χ^2 analysis or the Fisher exact test, where appropriate. The Pearson correlation coefficient was calculated to evaluate the associations of the duration of isoelectric activity, and of the DHCA, with the Vineland-II composite score. Multiple linear regression analysis was performed to test the effects of hypothermia, diagnosis, and duration of an isoelectric state on composite Vineland-II scores.

The F-test and standard diagnostic measures, such as residual plots, were used to check model adequacy and goodness-of-fit. Multicollinearity between predictor variables was assessed using multiple correlations. All statistics were completed using SPSS, version 21 (SPSS, Inc, Chicago,