Electroencephalography as a tool to predict cerebral oxygen metabolism during deep-hypothermic circulatory arrest in neonates with critical congenital heart disease

Gerard H. Laurent, ScB, Tiffany S. Ko, PhD, Kobina G. Mensah-Brown, MD, MS, Constantine D. Mavroudis, MD, MSC, MTR, Marin Jacobwitz, CRNP, PhD, Nicolina Ranieri, BSc, Susan C. Nicolson, MD, J. William Gaynor, MD, Wesley B. Baker, PhD, Daniel J. Licht, MD, Shavonne L. Massey, MD, MSCE, Jennifer M. Lynch, MD, PhD

PII: S2666-2736(23)00216-4
DOI: https://doi.org/10.1016/j.xjon.2023.08.004
Reference: XJON 846

To appear in: JTCVS Open

Received Date: 9 April 2023
Accepted Date: 1 August 2023

Please cite this article as: Laurent GH, Ko TS, Mensah-Brown KG, Mavroudis CD, Jacobwitz M, Ranieri N, Nicolson SC, Gaynor JW, Baker WB, Licht DJ, Massey SL, Lynch JM, Electroencephalography as a tool to predict cerebral oxygen metabolism during deep-hypothermic circulatory arrest in neonates with critical congenital heart disease, JTCVS Open (2023), doi: https://doi.org/10.1016/j.xjon.2023.08.004.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Copyright © 2023 The Authors. Published by Elsevier Inc. on behalf of The American Association for Thoracic Surgery
Electroencephalography as a tool to predict cerebral oxygen metabolism during deep-hypothermic circulatory arrest in neonates with critical congenital heart disease

Methods:
16 neonates with congenital heart disease (CHD) undergoing surgical repair had both bilateral centroparietal EEG leads and an optical probe attached to the head to measure cerebral electrical activity and cerebral oxygen saturation (ScO₂) respectively.

Results:
Quantitative EEG metrics are significantly associated with diffuse optical spectroscopy derived values of cerebral oxygen extraction fraction.

Implications:
EEG may be a useful tool for intraoperative neuromonitoring for neonates with CHD undergoing surgical repair. Decreases in ScO₂ during DHCA have been previously shown to correlate with increases in new post-operative white matter injury in MRI. EEG may help personalize cooling prior to DHCA to minimize the loss of ScO₂ during DHCA.
Electroencephalography as a tool to predict cerebral oxygen metabolism during deep-hypothermic circulatory arrest in neonates with critical congenital heart disease

Gerard H. Laurent, ScB, Tiffany S. Ko, PhD, Kobina G. Mensah-Brown, MD, MS, Constantine D. Mavroudis, MD, MSC, MTR, Marin Jacobwitz, CRNP, PhD, Nicolina Ranieri, BSc, Susan C. Nicolson, MD, J. William Gaynor, MD, Wesley B. Baker, PhD, Daniel J Licht, MD, Shavonne L. Massey, MD, MSCE, Jennifer M. Lynch, MD, PhD

Divisions of Neurology, Cardiothoracic Anesthesiology, Cardiothoracic Surgery, Children’s Hospital of Philadelphia, Philadelphia, PA 19104

There are no relevant disclosures to declare.

This study was supported by the NIH Grant Nos. NS-072338, NS-060653, HL-007954, HL-007915, P41-EB015893, the Congenital Heart Defect Coalition, and the June and Steve Wolfson Family foundation.

Corresponding author contact information: Gerard H. Laurent, 954-621-6467, Gerard_laurent@brown.edu

Article Word Count: 3451
**Glossary**

36 BSR = burst suppression ratio
37 CHD = congenital heart disease
38 CPB = cardiopulmonary bypass
39 CMRO$_2$ = Cerebral Oxygen Metabolism
40 DHCA = deep hypothermic circulatory arrest
41 EEG = electroencephalography
42 FD-DOS = frequency-domain diffuse optical spectroscopy
43 Hb = de-oxyhemoglobin
44 HbO$_2$ = oxyhemoglobin
45 OEF = oxygen extraction fraction
46 ScO$_2$ = cerebral oxygen saturation
47 SEF = spectral-edge frequency
48 SR = suppression ratio
total power
50 WMI = white matter injury
Central Picture Legend: Quantitative EEG metrics before circulatory arrest predict subsequent drop in cerebral O\textsubscript{2}.

Central Message: Quantitative EEG before deep hypothermic circulatory arrest (DHCA) predicts the extent of cerebral oxygen desaturation during DHCA in neonates with congenital heart disease undergoing surgical repair.

Perspective Statement: Neurological injury is common amongst neonates undergoing surgery for congenital heart disease. Recent research indicates that cerebral O\textsubscript{2} saturation decreases during circulatory arrest and these desaturation events are associated with brain injury. Here we show that EEG metrics before arrest can predict the extent of cerebral O\textsubscript{2} desaturation, providing a potentially useful tool for mitigating injury.

Abstract

Objectives: Recent research suggests that increased cerebral oxygen utilization during surgical intervention for neonates with congenital heart disease (CHD) may play a role in the development of post-operative white matter injury (WMI). The objective of this study is to determine whether increased cerebral electrical activity correlates with greater decrease of cerebral oxygen saturation during deep hypothermic circulatory arrest (DHCA).

Methods: Neonates with critical congenital heart disease requiring surgical intervention during the first week of life were studied. All subjects had continuous neuromonitoring with electroencephalography (EEG) and an optical probe (to quantify cerebral oxygen saturation, ScO\textsubscript{2}) during cardiac surgical repair that involved the use of cardiopulmonary bypass and deep hypothermic circulatory arrest (DHCA). A simple linear regression was used to investigate the association between EEG metrics before the DHCA period and the change in ScO\textsubscript{2} during the DHCA period.
**Results:** Sixteen neonates had both neuromonitoring modalities attached during surgical repair. ScO₂ data from 5 subjects were excluded due to poor data quality, yielding a total sample of 11 neonates. A simple linear regression model found that the presence of EEG activity at the end of cooling is positively associated with the decrease in ScO₂ that occurs during DHCA (p < 0.05).

**Conclusion:** EEG characteristics within 5 minutes before the initiation of DHCA may be useful in predicting the decrease in ScO₂ that occurs during DHCA. EEG may be an important tool for guiding cooling and the initiation of circulatory arrest to potentially decrease the prevalence of new WMI in neonates with critical CHD.

**Keywords:** Congenital heart disease, Deep hypothermic circulatory arrest, Cerebral oxygen extraction fraction, White matter injury, Neonate, Cerebral oxygen saturation, cardiopulmonary bypass

**Introduction:**
Infants born with complex congenital heart disease (CHD) requiring surgery during the neonatal period are at an increased risk for neurodevelopmental disabilities. Although the risk of neurologic injury may be due to numerous factors including abnormal in-utero brain development and genetic mutations, the perioperative period appears to be a time of acute vulnerability. Neonates undergoing deep hypothermic circulatory arrest (DHCA) for aortic arch reconstruction are at an increased risk for neurologic injury and subsequent poor outcomes. In these procedures,
Arch perfusion must be paused during surgical correction to maintain the absence of blood in the operative field. Cooling to deep hypothermic conditions is used to reduce the risk of brain injury that occurs due to a lack of perfusion and thus cerebral oxygen delivery during surgery. Despite the use of deep hypothermia, neurodevelopmental disabilities in children who have undergone neonatal cardiac surgery with arch reconstruction is common, with a population median IQ of 86 (significantly lower than average) and 30% requiring special education services. The development of neurologic deficits in this patient population may be partially attributable to the incidence of new post-operative white matter injury (WMI) that has been recently linked to ongoing cerebral oxygen metabolism (CMRO$_2$) during DHCA. Further research has found that cooling to the standard 18°C prior to initiation of circulatory arrest is insufficient in this patient population to induce isoelectric electroencephalography (EEG) patterns. These data indicate that clinically utilized efforts to reduce cerebral metabolism prior to circulatory arrest are likely insufficient. Improved neuromonitoring methods are needed to individualize cooling and perfusion methods to reduce cerebral oxygen demand to a sufficient level prior to initiation of DHCA.

EEG measures the electrical activity of the brain in real time and can provide clinically relevant insight into cerebral oxygen demand. Several metrics of electrical activity derived from EEG signals have been shown to correlate with other measures of CMRO$_2$. Three specific metrics have frequently been cited as markers of cerebral metabolic activity during instances of hypothermia or increasing anesthetic dosage: spectral-edge frequency (SEF95), total power (TP), and suppression ratio (SR). Although perfusion changes based on intraoperative EEG monitoring during cardiac surgery have been demonstrated to reduce neurologic deficits in adult
patients, its use has not been demonstrated to reduce the incidence of neurological injury in the neonatal and pediatric populations.\textsuperscript{14–16}

This study aims to utilize quantitative EEG metrics (SEF95, TP, and SR) as a tool to predict ongoing CMRO\textsubscript{2} (measured with a novel optical modality, frequency-domain diffuse optical spectroscopy (FD-DOS)) during DHCA. Establishing a potential relationship between pre-DHCA EEG suppression and ongoing CMRO\textsubscript{2} during DHCA could lead to individualized cooling for each patient with the goal of preventing peri-operative neurologic injury in neonates with CHD.

**Methods:**

This is a retrospective analysis of a prospectively studied cohort of full-term neonates with complex CHD who underwent surgical intervention requiring cardiopulmonary bypass (CPB) in the neonatal period at the Children’s Hospital of Philadelphia. The goal of the prospective study was to evaluate risk factors for development of brain WMI. While the prospective study cohort included patients enrolled between 2008 and 2018, this analysis was conducted on patients that were enrolled between 08/31/15-07/24/17. Study procedures were approved by the IRB at the Children’s Hospital of Philadelphia on August 08, 2011 (IRB number: 11-008191). Parents were approached for consent after birth and prior to day of surgery for pre- and postoperative MRI and perioperative EEG and optical monitoring. Participants were given the option to opt out of EEG monitoring but enroll in the larger study investigating the role of risk factors for development of brain WMI. Patients also concurrently provided informed written consent for the publication of their study data. Exclusion criteria were a birth weight less than 2 kg, a history of perinatal depression (i.e., 5-minute APGAR<5 or cord blood pH<7.0), perinatal seizures, evidence of end-
organ in
jury, pre-operative cardiac arrest, and significant preoperative intracerebral hemorrhage
(e.g., grade 3 or 4 intraventricular hemorrhage).
For this study, all subjects had subcutaneous bilateral centro-parietal EEG leads (C3, C4, P3, P4)
and an optical probe on the forehead placed for the duration of the surgery. FD-DOS data and
EEG data were captured continuously throughout the surgery. The surgeries of the 16 subjects in
this cohort were performed by 3 surgeons, although the majority were performed by a single
surgeon (12/16). Surgical strategy was the same for all subjects in this cohort. After
heparinization, the pulmonary artery and the right atrium are cannulated and CPB is commenced.
All study subjects were maintained on a combination of volatile (sevoflurane) and intravenous
anesthetic (ketamine, fentanyl). pH-stat blood gas management was used during cooling and
while hypothermic; alpha stat was used during rewarming and at normothermia per institutional
protocol. Systemic cooling is performed to a nasopharyngeal temperature of 18ºC for at least 15-
20 minutes and then circulatory arrest is initiated.

All subjects received a pre-operative MRI under general anesthesia on the day of surgery and an
unanesthetized post-operative MRI approximately one week after surgery. WMI in the
periventricular white matter was identified as T1 hyperintensity and conventionally rated using
the previously validated quadrant scoring system. Further MRI methodology has been
published elsewhere. The FD-DOS cerebral tissue oxygen saturation (ScO2) data has been
published, but a brief methodology is described here.

**Frequency-Domain Diffuse Optical Spectroscopy (FD-DOS):**
FD-DOS is a method to quantify tissue oxygenation that has been validated against MRI in
neonates. Specifically, multi-separation FD-DOS, used in the present study, is capable of
accurate quantification of $\text{ScO}_2$ \textit{i.e.}, in contrast to commercial oximeters, which use continuous wave near-infrared spectroscopy to monitor trends in saturation). FD-DOS uses the photon diffusion theory to relate the measured amplitude attenuation and phase shift of modulated and multiply scattered light detected on the tissue surface to the wavelength-dependent tissue absorption ($\mu_a$) and scattering ($\mu_s$) properties. The wavelength- and time-dependent absorption coefficient, $\mu_a(\lambda,t)$, depends linearly on the oxy- ([HbO$_2$]) and deoxyhemoglobin ([Hb]) concentration; thus measurements at multiple wavelengths yields these 2 parameters via linear absorption spectroscopy. From [HbO$_2$] and [Hb], we can derive the total hemoglobin concentration (THC = [HbO$_2$] + [Hb]) and ScO$_2$ (ScO$_2$ = [HbO$_2$]/THC). The oxygen extraction fraction (OEF), a surrogate marker for cerebral oxygen metabolism, can be calculated from the ScO$_2$ and arterial oxygen saturation measured clinically from an arterial blood gas sample.\textsuperscript{19} The DOS device used in the present study (Imagent, ISS Inc, Champaign, IL) is amplitude modulated at 110 MHz and uses source lasers at 2 wavelengths, 688 and 830 nm, with 1 detection fiber. We used 4 source-detector separations (1.5, 2.0, 2.5, and 3.0 cm along the tissue surface). The patient interface for this instrument consists of a custom made flexible black rubber probe secured to the subject’s forehead with a soft wrap.

\textbf{Electroencephalography (EEG):}

Four electrodes were placed subcutaneously to create two recording channels (C3-P3, C4-P4) according to the international 10-20 system prior to surgical repair. EEG leads were attached for the entirety of the procedure (baseline, cooling, circulatory arrest, and rewarming). EEG data were collected and stored on a CNS-310 Moberg monitor and then translated for analysis in MATLAB. Post-operatively, the EEG data went through a series of post-processing filters: a 0.5 Hz high pass, 30 Hz low pass, and a 60 Hz notch filter.
Despite the use of post-processing filters, there was considerable electrical artifact infiltrating the EEG signal due to clinician movement, the proximity of the optical probe on the head, and the presence of numerous electrical devices placed on the patient throughout surgery. All EEG data in this study were visually screened, first by a research assistant, and then subsequently by a pediatric epileptologist (S.M.) on CNS Envision software (Moberg Research, Inc, Ambler, PA) to ensure that data analyzed in the study did not contain electrical artifacts. The pediatric epileptologist discarded temporal periods of the EEG waveform that were non-physiologic. For example, EEG data including a supra-physiologically high amplitude (> 100 µV), or a repeating pattern of EEG signal (the same waveform repeating itself) over several seconds would be discarded. A single channel was analyzed for each patient. The channel with the least artifact was selected for analysis.

The presence of artifact in the EEG signal was pervasive. In order to gather consistent data from each patient, data were assessed at four five-minute epochs: baseline (any 5 minute time period before the start of cooling), end-cooling (within the last 5 minutes of cooling), end-arrest (within the last 5 minutes of DHCA), and post-rewarming (within the first 5 minutes after the end of rewarming). A minimum of 1 minute of continuous, artifact-free EEG data from each of these 4 epochs was analyzed for each subject.

We analyzed EEG data using 3 quantitative EEG metrics: suppression ratio (SR), total power (TP), and 95% spectral edge frequency (SEF95). Suppression ratio (SR) is defined as the proportion of time that the EEG signal is suppressed under a certain threshold. In this analysis, the threshold required to be considered in the SR was set at 5 microvolts, as neonatal EEG amplitudes below this threshold is considered a “severe burst suppression pattern”. Total power (TP) is the total energy of the EEG signal in nanowatts, which is measured by continuously
summing the power of each frequency (delta, theta, alpha, beta) over time. 95% Spectral Edge Frequency (SEF95) is the frequency below which 95% of the power spectrum is observed. The mean SR, TP, and SEF95 were calculated for each of the 4 epochs for every subject with at least 1 minute of artifact free data. SR was calculated using MATLAB. TP and SEF95 were calculated using CNS Envision software.

We examined the correlation between quantitative EEG parameters (SR, TP, SEF95) at the end of cooling with the change in cerebral oxygenation (ΔScO₂) during DHCA. We also sought to determine the correlation between quantitative EEG parameters at the end of cooling with the change in volume of WMI (post-operative WMI vs pre-operative WMI) reflected on MRI. We hypothesized that cooling-induced EEG suppression of high frequency brain activity and overall power would be correlated with lower CMRO₂ during DHCA (as reflected by minimal decrease in ScO₂). We also hypothesized that cooling induced EEG suppression would be correlated with a lower burden of WMI on post-operative MRI. A linear regression model was used to test these hypotheses.

We also examined the relationship between the magnitude of each EEG parameter at baseline, end-cooling, and post-rewarming with the oxygen extraction fraction (OEF) during the same epochs, hypothesizing that measures of increased cerebral activity would be associated with higher OEF (Figure 3). For instance, we compared each subject’s SEF at baseline, with that subject’s OEF calculation over the same period. This data, along with the analogous paired data for the other 2 epochs were plotted on a single scatter plot (comparing quantitative EEG values to OEF). To test our hypothesis, we used a mixed effects linear regression model with patient identification as the grouping variable to minimize the presence of intra-subject variability.

Oxygen extraction fraction is the outcome variable and SEF95, TP, and SR are each separately
predictor variables. Only baseline, end-cooling, and post-rewarming were chosen because the OEF calculation during the DHCA period is not meaningful as blood flow is zero (conditions are not in steady state). For the linear regression and mixed effects linear regression models, statistical tests for a slope different from zero were done using a t-statistic, and a p value of <0.05 was deemed to represent statistical significance. Summary statistics are presented using medians and interquartile ranges.

**Results**

In this study, we obtained EEG data from 16 subjects undergoing CPB with the use of DHCA for cardiac repair. All 16 subjects had at least one minute of usable EEG data for the 4 epochs analyzed. Of these 16, however, five subjects had unusable FD-DOS data due to poor data quality, which yields 11 subjects with both FD-DOS and EEG data. Therefore, data solely describing quantitative EEG changes represent 16 subjects (Figure 1), and data describing associations between EEG and OEF or ScO\(_2\) represent 11 subjects (Figures 2 and 3). The median cooling time prior to DHCA was 17.05 minutes (IQR [15.53, 29.18]). The median DHCA duration was 38.78 minutes (IQR [30.10, 46.17]), while the median total time on CPB (excluding DHCA duration) was 39.58 (IQR [37.22, 52.10]). The median temperature at which End-Cooling EEG activity was extracted was 19.5°C (IQR [18.58 °C, 20.4 °C]); the lowest temperature was 17.35 °C and the highest temperature was 22.08 °C. At our institution, temperatures falling within 18 °C to 22 °C are adequate to initiate DHCA, and thus cooling was fully complete during the End-Cooling EEG activity assessments. Patient demographic data is summarized in Table 1.

**Intraoperative EEG Changes**
SEF95: SEF95 decreases during the cooling period (indicating greater EEG suppression) and remains depressed through the end of rewarming (Figure 1a). SEF95 is higher during the post-rewarming epoch than during the end-cooling and end-arrest epochs, but lower than baseline. The median SEF95 values vary from 5.00 Hz (IQR [3.11, 5.86]), 1.114 Hz (IQR [0.88, 1.71]), 0.791 Hz (IQR [0.67, 1.40]), and 1.698 Hz (IQR [1.41, 2.38]) through the baseline, end-cooling, end-arrest, and post-rewarming periods respectively.

TP: EEG total power (TP) follows the same trend as the SEF95 changes over time (Figure 1b). Median total power values from each epoch were 0.09 nW (IQR [0.049, 0.361]), 0.01 nW (IQR [0.004, 0.108]), 0.004 nW (IQR [0.002, 0.012]), and 0.022 nW (IQR [0.011, 0.052]) for the baseline, end-cooling, end-arrest, and post-rewarming periods respectively.

SR: The EEG SR increases significantly after cooling (indicating greater EEG suppression) and then remains elevated above baseline levels through the end of rewarming (Figure 1c). The median SR increases from 0.487 (IQR [0.383, 0.605]), to 0.942 (IQR [0.739, 0.978]), 0.9729 (IQR [0.877, 0.989]), and 0.866 (IQR [0.787, 0.937]) through the baseline, end-of-cooling, end-of-arrest, and post-rewarming periods respectively.

Correlation with pre-arrest EEG and cerebral oxygen extraction during arrest

ScO2 decreased during DHCA, with a median change of -38.52% (IQR [-31.35, -51.71]). Each EEG parameter immediately prior to initiation of DHCA was significantly correlated with ΔScO2 during DHCA (SEF95: P = 0.021, R² = 0.402, TP: P = 0.025, R² = 0.445, SR: P = 0.027, R² = 0.436) (Error! Reference source not found.).

Correlation of EEG Parameters to Oxygen Extraction Fraction
SEF95 (Figure 3a), TP (Figure 3b), and SR (Figure 3c) during the baseline, end-cooling, and post-rewarming epochs were all associated with concurrent OEF data (p < 0.001, p = 0.012, and p = 0.049, respectively) (Table 2).

**Correlation with post-operative injury on MRI**

Of the 9 subjects with pre- and post-operative MRI measurements, the median volume of new WMI on post-operative MRI was 19.38 mm$^3$ (IQR [5.22, 86.83]). Three subjects were observed to have pre-operative WMI, with a median volume of 22.71 mm$^3$ (IQR [10.9, 31.85]). No significant or trending correlations were observed between quantitative EEG metrics at the end of cooling and new post-operative WMI.

**Discussion**

This study demonstrates that the use of EEG during neonatal cardiac surgery can produce several quantitative EEG parameters that give insight into CMRO$_2$. Specifically, SEF95, TP, and SR were found to correlate with OEF throughout the intraoperative period (Figure 3). We have demonstrated that high levels of EEG suppression (low SEF95, low TP, and high SR) are significantly associated with lower levels of cerebral oxygen extraction. Furthermore, these EEG parameters prior to the initiation of DHCA predicted the amount of cerebral oxygen desaturation during DHCA (Figure 2), highlighting the potential usefulness of EEG for patient-specific cooling goals. Because this study was a retrospective analysis of neonatal EEG activity and cerebral oxygenation and not a controlled experiment, we cannot exclude the role of other postoperative variables in contributing to ongoing cerebral oxygen desaturation.

EEG guided reduction of CMRO$_2$ has been linked to a decrease in the prevalence of adverse neurologic outcomes in adult patients undergoing cardiac surgery, but EEG neuromonitoring is...
not used as standard of care during neonatal cardiac surgery in many institutions.\textsuperscript{21,22} One such previous study found statistically significant decreases in neurologic sequelae, length of stay in the hospital, and estimated overall hospital expenditure in pediatric patients undergoing EEG monitoring during repair of CHD compared to patients without EEG neuromonitoring.\textsuperscript{23} The results presented herein (Figure 2) provide evidence that EEG parameters (SEF95, TP, and SR) prior to the initiation of DHCA can predict the degree of ongoing CMRO\textsubscript{2} during DHCA. Given recent research establishing that ongoing cerebral metabolism during DHCA is associated with increased postoperative WMI\textsuperscript{4}, our data suggests that quantitative EEG metrics can provide greater insight into the intraoperative causes of WMI and serve as a potential biomarker for therapeutic intervention (i.e. CPB pump flow increases, increasing FiO\textsubscript{2}, increasing cooling duration, increasing anesthetic dosages, etc.).

We sought to establish which EEG parameter would be most correlated to cerebral oxygen consumption. SEF95 and TP both correlate negatively with intraoperative anesthetic dosage and positively with nasopharyngeal temperature in adult patients, suggesting that these metrics can be useful for extrapolating cerebral functional activity.\textsuperscript{10,11,13} The EEG suppression ratio (SR) or burst suppression ratio (BSR) quantifies the percentage of an EEG signal that has very low voltage.\textsuperscript{25} The SR increases when the brain exhibits a characteristic EEG pattern termed burst suppression.\textsuperscript{26} Burst suppression occurs during periods of brain inactivation such as general anesthesia, deep hypothermia, or brain injury.\textsuperscript{11,26} Prior research consistently reveals that pediatric EEG during cardiac surgery becomes more suppressed during cooling and more active during rewarming periods of CPB.\textsuperscript{8,24,27} Both SEF95 and TP exhibited this pattern in Figure 1, suggesting that they are sensitive to the same cerebral
electrical activity changes. SR increased after baseline but did not appear significantly different after that. The lack of differentiation in SR during other epochs may be an indication that SR is less sensitive to functional brain activity than SEF95 and TP. Furthermore, while all 3 quantitative EEG metrics exhibited a statistically significant correlation to FD-DOS derived OEF values according to a mixed effects linear regression model, SR was the least statistically significant with a p-value of 0.049 compared to < 0.001 and 0.012 for SEF95 and TP, respectively (Table 2). Given that SEF95 is a significantly better predictor of OEF than TP and SR, it should be further studied as an EEG metric used to assess cerebral activity. There are several studies that suggest that prolonged time under DHCA is a risk factor for various forms of neurologic injury such as post-operative seizures, new WMI, and neurodevelopmental delays. There are alternative perfusion strategies to DHCA that are predominant in the current era, but DHCA is still used by a subset of surgeons, and brief periods of DHCA are still sometimes necessary even if not utilized for the majority of repair. A potential confounding variable in the correlation between the end cooling EEG metrics and the ΔScO\textsubscript{2} during DHCA is the duration of DHCA. A linear regression analysis found a trending negative correlation between the duration of DHCA and the change in ΔScO\textsubscript{2} during DHCA (p = 0.09, R\textsuperscript{2} = 0.285). That is, those subjects with longer DHCA times tended to have a greater decrease in cerebral oxygen saturation during DHCA. A major limitation of EEG is the presence of artifact infiltrating the signal. In this study, artifact caused by electrical devices in the OR and movement in the operative field reduced the availability of usable data. To gather data, filtered EEG signal had to be manually screened by a pediatric epileptologist (S.M.). Given the need to manually screen for artifact, only 4 discrete time periods were chosen for screening per subject. Although EEG was manually screened for
artifacts herein by a well-trained epileptologist, in the future, automated EEG algorithms to identify and remove artifacts promise to allow clinicians to visualize quantitative EEG metrics in real-time (i.e., no post-hoc analysis needed).

Another major limitation of this study is the small sample size. Although 16 patients had both EEG and FD-DOS attached to the head for the entire procedure, FD-DOS probe displacement reduced the number of subjects with both neuromonitoring modalities to 11. Because of the small sample size, one subject (highlighted in yellow in Figure 2) had a disproportionate influence on the correlation between end-cooling EEG activity and ΔScO₂ during DHCA. This subject’s SEF95 immediately before DHCA, (SEF95 = 3.74), was more than twice that of the study population’s mean, (SEF95\text{mean} = 1.38). If this subject were to be excluded from the linear regression analyses shown in Figure 2, the relationships between end-cooling SEF95, TP, and SR with ΔScO₂ during DHCA would not be significant (p = 0.231, p = 0.13, p = 0.296 respectively). However, because the data quality was adequate, we included this subject in all analyses.

Another consequence of this study’s small sample size is the lack of any correlation between end-cooling EEG metrics and the occurrence of new WMI in post-operative MRI. Although there is EEG data for 16 subjects, pre and post-operative MRI data is only available for 9 subjects (of which only 7/9 had both FD-DOS and EEG data). Furthermore, most subjects experienced only small increases in the volume of WMI, making it difficult to do a linear regression analysis. Our results motivate a larger study to investigate the relationship between intraoperative EEG and post-operative WMI.

Conclusion
EEG is a useful tool for intraoperative neuromonitoring and can give insight into the efficacy of cooling for decreasing CMRO$_2$. These findings, combined with our prior findings that increased cerebral oxygen metabolism during DHCA is associated with increased WMI, suggest that EEG guided cooling (by increasing the duration of cooling to ensure electrocerebral silence) may help to individualize and optimize pre-DHCA cooling to reach the cerebral metabolic nadir (Figure 4). In doing so, the data suggest a potential for decreasing the risk of hypoxic ischemic injury in neonates undergoing complex congenital cardiac surgery with DHCA.

References


Table 1 Patient demographics; HLHS – hypoplastic left heart syndrome; MS – mitral stenosis; AS – atrial stenosis; AA – atrial atresia; MA - mitral atresia; AVC – atrioventricular canal; DILV – double inlet left ventricle; TGA – transposition of the great arteries

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EEG</th>
<th>EEG and FD-DOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Age at Surgery (days)</td>
<td>5 [2.8, 5]</td>
<td>5 [2, 5]</td>
</tr>
<tr>
<td>Birth Weight (kg)</td>
<td>3.24 [3.3, 3.8]</td>
<td>3.17 [3.0, 3.6]</td>
</tr>
<tr>
<td>Head Circumference (cm)</td>
<td>34.15 [33.4, 34.9]</td>
<td>34 [33.2, 35.3]</td>
</tr>
<tr>
<td>Female, n</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>MRI Completed, n</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Primary Heart Defect N, (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLHS (MA/AA)</td>
<td>3, (19)</td>
<td>3, (27)</td>
</tr>
<tr>
<td>HLHS (MS/AS)</td>
<td>1, (6)</td>
<td>0</td>
</tr>
<tr>
<td>HLHS (MS/AA)</td>
<td>4, (25)</td>
<td>2, (18)</td>
</tr>
<tr>
<td>Aortic Arch hypoplasia</td>
<td>4, (25)</td>
<td>2, (18)</td>
</tr>
<tr>
<td>AVC</td>
<td>2, (13)</td>
<td>2, (18)</td>
</tr>
<tr>
<td>DILV</td>
<td>1, (6)</td>
<td>1, (9)</td>
</tr>
<tr>
<td>d-TGA</td>
<td>1, (6)</td>
<td>1, (9)</td>
</tr>
</tbody>
</table>

Table 2 Results from 3 mixed effects linear regression models in which oxygen extraction fraction is the outcome variable and SEF95, TP, and SR are each separately predictor variables. These data correspond to the lines of best fit plotted in Figure 3.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (SE)</th>
<th>T Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEF95</td>
<td>0.061 (0.017)</td>
<td>3.630</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Intercept</td>
<td>0.276 (0.046)</td>
<td>6.007</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>TP</td>
<td>0.050 (0.018)</td>
<td>2.719</td>
<td>0.011</td>
</tr>
<tr>
<td>Intercept</td>
<td>0.596 (0.070)</td>
<td>8.560</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SR</td>
<td>-0.231 (0.113)</td>
<td>-2.04</td>
<td>0.049</td>
</tr>
<tr>
<td>Intercept</td>
<td>0.598 (0.082)</td>
<td>7.307</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Legends

Table 1: Patient demographics; HLHS – hypoplastic left heart syndrome; MS – mitral stenosis; AS – atrial stenosis; AA – atrial atresia; MA - mitral atresia; AVC – atrioventricular canal; DILV – double inlet left ventricle; TGA – transposition of the great arteries

Table 2: Results from 3 mixed effects linear regression models in which oxygen extraction fraction is the outcome variable and SEF95, TP, and SR are each separately predictor variables. These data correspond to the lines of best fit plotted in Figure 3.

Figure 1: Three boxplots showing the change in (a) spectral edge frequency 95, (b) total power, and (c) suppression ratio over the course of surgery for 16 subjects. Significance is determined by pairwise Wilcoxon signed-rank tests between timepoints. Significance is Bonferroni adjusted to an alpha level of 0.0083; significant differences (adjusted p-value < 0.05) are indicated by horizontal black lines. The lower and upper borders of each box represent the lower and upper quartiles (25th percentile and 75th percentile). The middle horizontal line represents the median. The lower and upper whiskers represent the minimum and maximum values of non-outliers. Outliers (indicated by red plus signs) are defined as values greater than \( q_3 + (2.7 \times \sigma) \times (q_3 - q_1) \) or less than \( q_1 - (2.7 \times \sigma) \times (q_3 - q_1) \); \( q_1 \) = first quantile, \( q_3 \) = third quantile, \( \sigma \) = standard deviation.

Figure 2: End Cooling EEG vs DHCA ΔScO2: Scatter plots indicating the value of three quantitative EEG metrics: (a) spectral edge frequency 95%, (b) total power, and (c) suppression ratio at the end of cooling (prior to DHCA) compared to the subject’s change in ScO\(_2\) during DHCA. Black lines of best fit are plotted in (a), (b), and (c). Gray shaded error bars represent the 95% confidence interval for the results of the linear regression model. Each dot color corresponds to a different subject. Results of a simple line regression model revealed that every quantitative EEG metric at the end of cooling is a significant predictor of ΔScO2 during DHCA.

Figure 3: Scatter plots of the a) spectral edge frequency 95% (Hz), b) total power (nW), and c) suppression ratio versus the oxygen extraction fraction for every subject at baseline, end-cooling, and post-rewarming. A mixed effects linear regression model was used to generate a thick black line plotting the model estimated OEF vs given quantitative EEG values in all 3 subplots. 95% confidence intervals from the model are indicated by gray shaded error bars. The model revealed that SEF95, TP, and SR are significant predictors of OEF. The x-axis in b) is log scaled for better visualization given the large number of near 0 total power values. Each dot color corresponds to a different subject (3 measures for each subject; baseline, end-cooling and post rewarming).

Figure 4: Quantitative EEG metrics are significantly correlated with cerebral OEF (a marker of cerebral metabolism) calculated from diffuse optical spectroscopy (left). Furthermore, quantitative EEG metrics within the 5 minutes before the initiation of DHCA predict the decrease in ScO\(_2\) that occurs during DHCA (right). a), b), and c) represent the quantitative EEG metric on the x axis for each scatter plot. a): spectral edge frequency 95% (Hz), b): total power (nW), c): suppression ratio. OEF: oxygen extraction fraction, ScO\(_2\): cerebral oxygen saturation, DHCA: deep hypothermic circulatory arrest.
Electroencephalography as a tool to predict cerebral oxygen metabolism during deep-hypothermic circulatory arrest in neonates with critical congenital heart disease

Methods:
16 neonates with congenital heart disease (CHD) undergoing surgical repair had both bilateral centroparietal EEG leads and an optical probe attached to the head to measure cerebral electrical activity and cerebral oxygen saturation ($\text{ScO}_2$) respectively.

Results:
Quantitative EEG metrics are significantly associated with diffuse optical spectroscopy derived values of cerebral oxygen extraction fraction. Each color is a subject, and each subject has 3 dots corresponding to 3 time points during surgical repair. Quantitative EEG metrics within the 5 minutes before the start of deep hypothermic circulatory arrest (DHCA) predict the decrease in $\text{ScO}_2$ during DHCA.

Implications:
EEG may be a useful tool for intraoperative neuromonitoring for neonates with CHD undergoing surgical repair. Decreases in $\text{ScO}_2$ during DHCA have been previously shown to correlate with increases in new post-operative white matter injury in MRI. EEG may help personalize cooling prior to DHCA to minimize the loss of $\text{ScO}_2$ during DHCA.
The graph shows the relationship between \( \Delta \text{ScO}_2 \) during DHCA and two different metrics: Spectral Edge (Hz) on the left and Total Power (nW) on the right. For the Spectral Edge (Hz) metric:

- \( p = 0.02 \)
- \( R^2 = 0.40 \)

For the Total Power (nW) metric:

- \( p = 0.03 \)
- \( R^2 = 0.38 \)