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

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ABSTRACT

Objectives: Recent research suggests that increased cerebral oxygen use during surgical intervention for neonates with congenital heart disease may play a role in the development of postoperative white matter injury. 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.
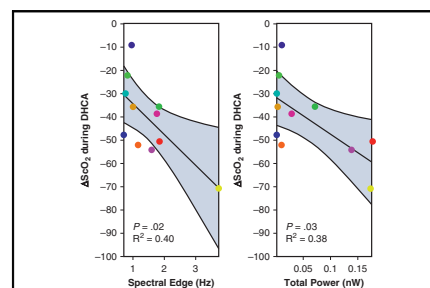
Methods: Neonates with critical congenital heart disease requiring surgical intervention during the first week of life were studied. All subjects had continuous neuromonitoring with electroencephalography and an optical probe (to quantify cerebral oxygen saturation) during cardiac surgical repair that involved the use of cardiopulmonary bypass and deep hypothermic circulatory arrest. A simple linear regression was used to investigate the association between electroencephalography metrics before the deep hypothermic circulatory arrest period and the change in cerebral oxygen saturation during the deep hypothermic circulatory arrest period.

Results: Sixteen neonates had both neuromonitoring modalities attached during surgical repair. Cerebral oxygen saturation 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 electroencephalography activity at the end of cooling is positively associated with the decrease in cerebral oxygen saturation that occurs during deep hypothermic circulatory arrest ($P < .05$).

Conclusions: Electroencephalography characteristics within 5 minutes before the initiation of deep hypothermic circulatory arrest may be useful in predicting the decrease in cerebral oxygen saturation that occurs during deep hypothermic circulatory arrest. Electroencephalography may be an important tool for guiding cooling and the initiation of circulatory arrest to potentially decrease the prevalence of new white matter injury in neonates with critical congenital heart disease. (JTCVS Open 2023;16:801-9)

Quantitative EEG metrics before circulatory arrest predict a subsequent decrease in cerebral oxygen.

CENTRAL MESSAGE

Quantitative EEG before DHCA predicts the extent of cerebral oxygen desaturation during DHCA in neonates with CHD undergoing surgical repair.

PERSPECTIVE

Neurologic injury is common among neonates undergoing surgery for CHD. Recent research indicates that cerebral oxygen saturation decreases during circulatory arrest and that these desaturation events are associated with brain injury. We show that EEG metrics before arrest can predict the extent of cerebral oxygen desaturation, providing a potentially useful tool for mitigating injury.

Infants born with complex congenital heart disease (CHD) requiring surgery during the neonatal period are at an increased risk for neurodevelopmental disabilities.[1] 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.[2-5]

Abbreviations and Acronyms

CHD	=	congenital heart disease
$CMRO_2$	=	cerebral oxygen metabolism
CPB	=	cardiopulmonary bypass
DHCA	=	deep hypothermic circulatory arrest
EEG	=	electroencephalography
FD-DOS	=	frequency-domain diffuse optical spectroscopy
Hb	=	de-oxyhemoglobin
HbO_2	=	oxyhemoglobin
IQR	=	interquartile range
MRI	=	magnetic resonance imaging
OEF	=	oxygen extraction fraction
ScO_2	=	cerebral oxygen saturation
SEF	=	spectral-edge frequency
SR	=	suppression ratio
TP	=	total power
WMI	=	white matter injury

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.[6]

The development of neurologic deficits in this patient population may be partially due to the incidence of new postoperative white matter injury (WMI) that has been recently linked to ongoing cerebral oxygen metabolism ($CMRO_2$) during DHCA.[4] Further research has found that cooling to the standard 18 °C before initiation of circulatory arrest is insufficient in this patient population to induce isoelectric electroencephalography (EEG) patterns.[7] These data indicate that clinically used efforts to reduce cerebral metabolism before 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 before 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 $CMRO_2$.[8] Three specific metrics have 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).[9-12] 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.[13-15]

This study aims to use quantitative EEG metrics (SEF95, TP, and SR) as a tool to predict ongoing $CMRO_2$ (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 $CMRO_2$ during DHCA could lead to individualized cooling for each patient with the goal of preventing perioperative neurologic injury in neonates with CHD.

MATERIALS AND 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. Although the prospective study cohort included patients enrolled between 2008 and 2018, this analysis was conducted on patients that were enrolled between August 31, 2015, to July 24, 2017. Study procedures were approved by the Institutional Review Board at the Children's Hospital of Philadelphia on August 8, 2011 (Number: 11-008191). Parents were approached for consent after birth and before the day of surgery for preoperative and postoperative magnetic resonance imaging (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 (ie, 5-minute APGAR<5 or cord blood pH<7.0), perinatal seizures, evidence of end-organ injury, preoperative cardiac arrest, and significant preoperative intracerebral hemorrhage (eg, 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 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 18 °C for at least 15 to 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 postoperative MRI approximately 1 week after surgery. WMI in the periventricular white matter was identified as T1 hyperintensity and conventionally rated using the previously validated quadrant scoring system.[16] Further MRI methodology has been published.[4,17] The FD-DOS cerebral tissue oxygen saturation (ScO_2) data have been published, but a brief methodology is described here.[4]

Frequency-Domain Diffuse Optical Spectroscopy

FD-DOS is a method to quantify tissue oxygenation that has been validated against MRI in neonates.[18] Specifically, multi-separation FD-DOS, used in the present study, is capable of accurate quantification of ScO_2 (ie, 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 (μ_a) and scattering (μ'_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 $CMRO_2$, can be calculated from the ScO_2 and arterial oxygen saturation measured clinically from an arterial blood gas sample.[18] The DOS device used in the present study (Imagent, ISS Inc, Champaign, Ill) 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.

Electroencephalography

Four electrodes were placed subcutaneously to create 2 recording channels (C3-P3, C4-P4) according to the international 10 to 20 system before 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. Postoperatively, the EEG data went through a series of postprocessing filters: a 0.5 Hz high pass, 30 Hz low pass, and a 60 Hz notch filter.

Despite the use of postprocessing 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) 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 nonphysiologic. 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. To gather consistent data from each patient, data were assessed at four 5-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 postrewarming (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 were analyzed for each subject.

We analyzed EEG data using 3 quantitative EEG metrics: SR, TP, and SEF95. 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 μV, as neonatal EEG amplitudes below this threshold is considered a "severe burst suppression pattern".[19] 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. 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 ΔScO_2 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 (postoperative WMI vs preoperative WMI) reflected on MRI. We hypothesized that cooling-induced EEG suppression of high frequency brain activity and overall power would be correlated with lower $CMRO_2$ during DHCA (as reflected by minimal decrease in ScO_2). We also hypothesized that cooling induced EEG suppression would be correlated with a lower burden of WMI on postoperative 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 postrewarming with the OEF during the same epochs, hypothesizing that measures of increased cerebral activity would be associated with higher OEF (Figure 1). For instance, we compared each subject's SEF at baseline, with that subject's OEF calculation over the same period. These 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 postrewarming were chosen because the OEF calculation during the DHCA period is not meaningful because 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. Summary statistics are presented using medians and interquartile ranges (IQRs).

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 1 minute of usable EEG data for the 4 epochs analyzed. Of these 16, 5 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 2), and data describing associations between EEG and OEF or ScO_2 represent 11 subjects (Figures 1 and 3). The median cooling time before 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, 18.58-20.4 °C); the lowest temperature was 17.35 °C, and the highest temperature was 22.08 °C. At our institution, temperatures within 18 to 22 °C are adequate to initiate DHCA, and thus cooling was fully complete during the end-cooling EEG activity assessments. Patient demographic data are summarized in Table 1.

Intraoperative Electroencephalography Changes

SEF95 decreases during the cooling period (indicating greater EEG suppression) and remains depressed through
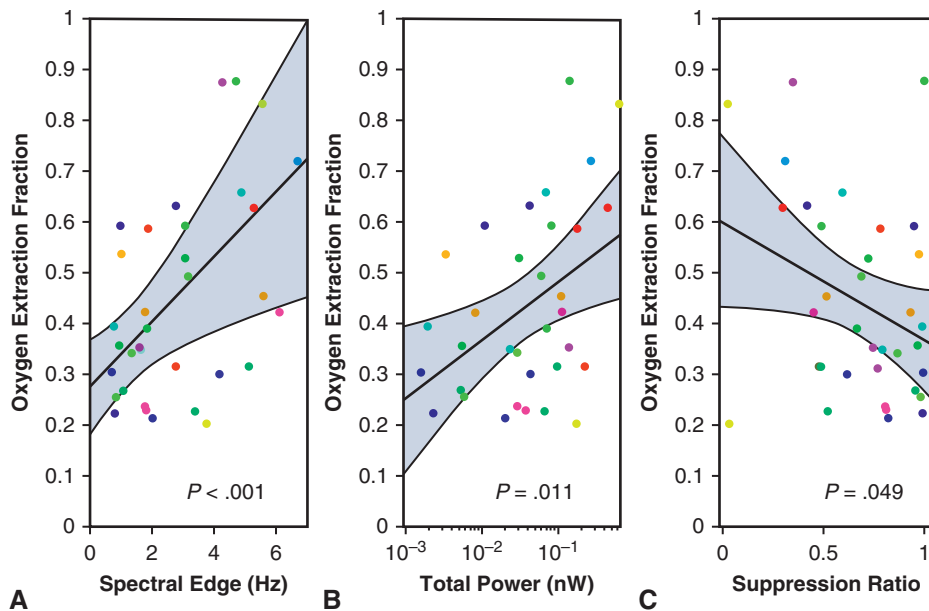
FIGURE 1. Scatter plots of the (A) spectral edge frequency 95% (Hz), (B) TP (nW), and (C) SR versus the OEF for every subject at baseline, end-cooling, and postrewarming. A mixed effects linear regression model was used to generate a thick *black line* plotting the model estimated OEF versus given quantitative EEG values in all 3 subplots. The 95% CIs from the model are indicated by *blue 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 TP values. Each *dot color* corresponds to a different subject (3 measures for each subject; baseline, end-cooling and post rewarming).

the end of rewarming (Figure 2, *A*). SEF95 is higher during the postrewarming 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 postrewarming periods, respectively.

EEG TP follows the same trend as the SEF95 changes over time (Figure 2, *B*). 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 postrewarming periods, respectively.

The EEG SR increases significantly after cooling (indicating greater EEG suppression) and then remains elevated above baseline levels through the end of rewarming (Figure 2, *C*). 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 postrewarming periods, respectively.

Correlation With Prearrest Electroencephalography and Cerebral Oxygen Extraction During Arrest

ScO_2 decreased during DHCA, with a median (IQR, −31.35 to −51.71).change of −38.52%. Each EEG

parameter immediately before initiation of DHCA was significantly correlated with ΔScO_2 during DHCA (SEF95: $P = .021$, $R^2 = 0.402$, TP: $P = .025$, $R^2 = 0.445$, SR: $P = .027$, $R^2 = 0.436$) (Figure 3).

Correlation of Electroencephalography Parameters to Oxygen Extraction Fraction

SEF95 (Figure 1, *A*), TP (Figure 1, *B*), and SR (Figure 1, *C*) during the baseline, end-cooling, and postrewarming epochs were all associated with concurrent OEF data ($P < .001$, $P = .012$, and $P = .049$, respectively) (Table 2).

Correlation With Postoperative Injury on Magnetic Resonance Imaging

Of the 9 subjects with preoperative and postoperative MRI measurements, the median volume of new WMI on postoperative MRI was 19.38 mm^3 (IQR, 5.22-86.83). Three subjects were observed to have preoperative 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 postoperative 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
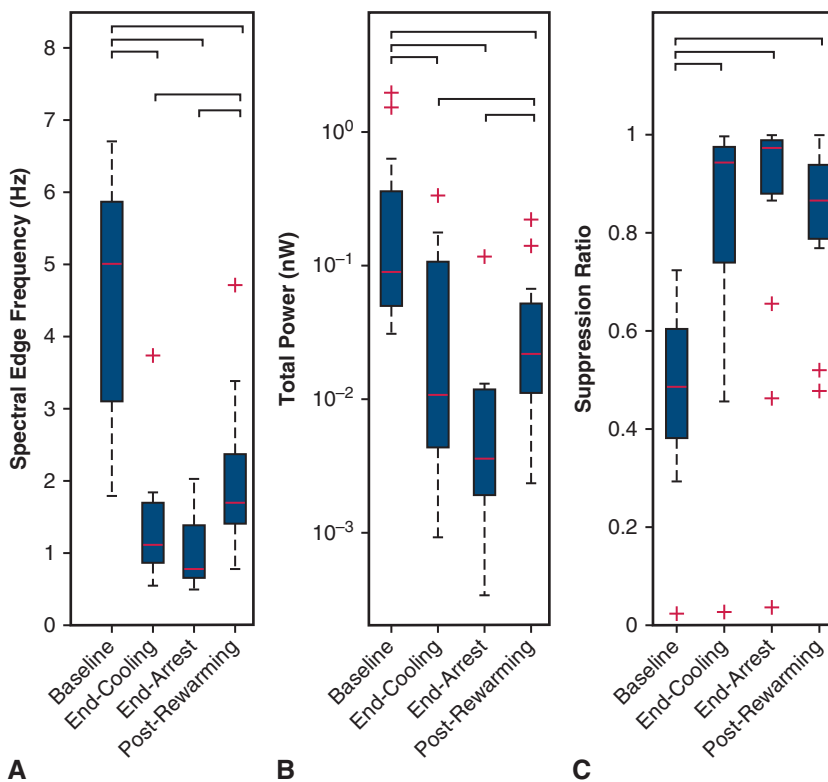
FIGURE 2. Three boxplots showing the change in (A) spectral edge frequency 95, (B) TP, and (C) SR over the course of surgery for 16 subjects. Significance is determined by pairwise Wilcoxon signed-rank tests between timepoints. Significance is Bonferroni adjusted to an alpha level of 0.0083; significant differences (adjusted *P* value < .05) are indicated by *horizonal 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 nonoutliers. Outliers (indicated by *red* plus signs) are defined as values greater than $q_3 + (2.7 * \sigma) * (q_3 - q_1)$ or less than $q_1 - (2.7 * \sigma) * (q_3 - q_1)$; q_1 = first quantile, q_3 = third quantile, σ = standard deviation.

throughout the intraoperative period (Figure 1). 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 before the initiation of DHCA predicted the amount of cerebral oxygen desaturation during DHCA (Figure 3), 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.[13,14] 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 with patients without EEG neuromonitoring.[20] The results

presented herein (Figure 3) provide evidence that EEG parameters (SEF95, TP, and SR) before the initiation of DHCA can predict the degree of ongoing $CMRO_2$ during DHCA. Given recent research establishing that ongoing cerebral metabolism during DHCA is associated with increased postoperative WMI,[4] our data suggest that quantitative EEG metrics can provide greater insight into the intraoperative causes of WMI and serve as a potential biomarker for therapeutic intervention (ie CPB pump flow increases, increasing FiO_2, increasing cooling duration, increasing anesthetic dosages).

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.[9,10,12] The EEG SR or burst SR quantifies the percentage of an EEG signal that has low voltage.[21] The SR increases when the brain exhibits a characteristic EEG pattern termed burst suppression.[11] Burst suppression occurs during periods of brain inactivation such as general anesthesia, deep hypothermia, or brain injury.[10,11]
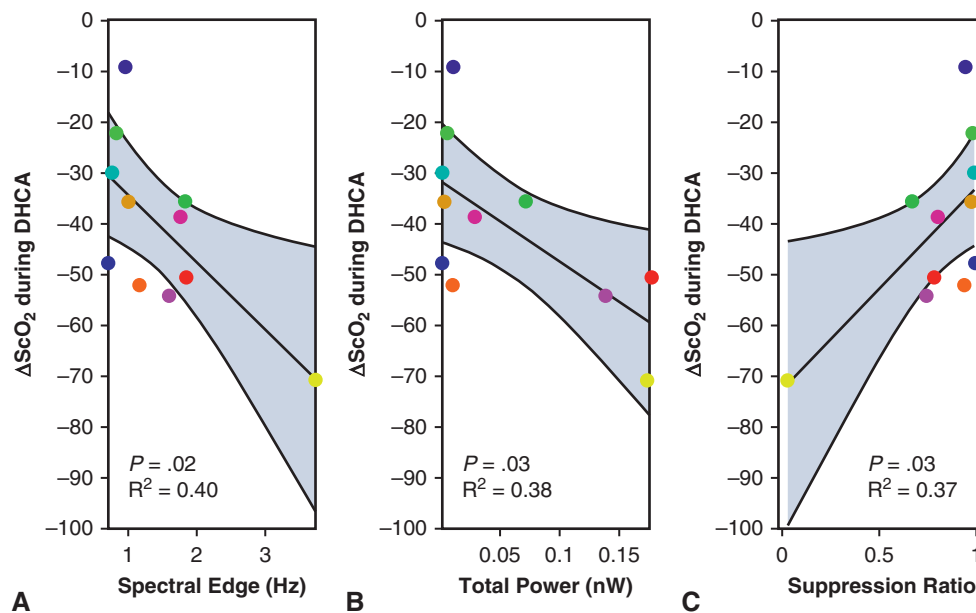
FIGURE 3. End-cooling EEG versus DHCA ΔScO2: Scatter plots indicating the value of 3 quantitative EEG metrics: (A) spectral edge frequency 95%, (B) TP, and (C) SR at the end of cooling (before DHCA) compared with the subject's change in ScO_2 during DHCA. *Black lines* of best fit are plotted in (A), (B), and (C). *Blue shaded* error bars represent the 95% CI for the results of the linear regression model. Each *dot color* corresponds to a different subject. Results of a simple linear regression model revealed that every quantitative EEG metric at the end of cooling is a significant predictor of ΔScO2 during DHCA. ScO_2, Cerebral oxygen saturation.

Prior research consistently reveals that pediatric EEG during cardiac surgery becomes more suppressed during cooling and more active during rewarming periods of CPB.[7,22,23] Both SEF95 and TP exhibited this pattern in Figure 2, 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, although 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.049 compared with less than .001 and .012 for SEF95 and TP, respectively (Table 2). Given that SEF95 is a significantly better

TABLE 1. Patient demographics

Patient variables	EEG	EEG and FD-DOS
N	16	11
Age at surgery (d)	5 [2.8, 5]	5 [2, 5]
Birth weight (kg)	3.24 [3.3, 3.8]	3.17 [3.0, 3.6]
Head circumference (cm)	34.15 [33.4, 34.9]	34 [33.2, 35.3]
Female, n	5	2
MRI completed, n	9	7
Primary heart defect N, (%)		
HLHS (MA/AA)	3 (19)	3 (27)
HLHS (MS/AS)	1 (6)	0
HLHS (MS/AA)	4 (25)	2 (18)
Aortic arch hypoplasia	4 (25)	2 (18)
AVC	2 (13)	2 (18)
DILV	1 (6)	1 (9)
d-TGA	1 (6)	1 (9)

EEG, Electroencephalography; *FD-DOS,* frequency-domain diffuse optical spectroscopy; *MRI,* magnetic resonance imaging; *HLHS,* hypoplastic left heart syndrome; *MA,* mitral atresia; *AA,* atrial atresia; *MS,* mitral stenosis; *AS,* atrial stenosis; *AVC,* atrioventricular canal; *DILV,* double inlet left ventricle; *d-TGA,* dextro-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

Parameter	Estimate (SE)	T value	P value
SEF95	0.061 (0.017)	3.630	<.001
Intercept	0.276 (0.046)	6.007	<.001
TP	0.050 (0.018)	2.719	.011
Intercept	0.596 (0.070)	8.560	<.001
SR	−0.231 (0.113)	−2.04	.049
Intercept	0.598 (0.082)	7.307	<.001

These data correspond to the lines of best fit plotted in Figure 1. *SE*, Standard error; *SEF*, spectral edge frequency; *TP*, total power; *SR*, suppression ratio.

predictor of OEF than TP and SR, it should be further studied as an EEG metric used to assess cerebral activity.
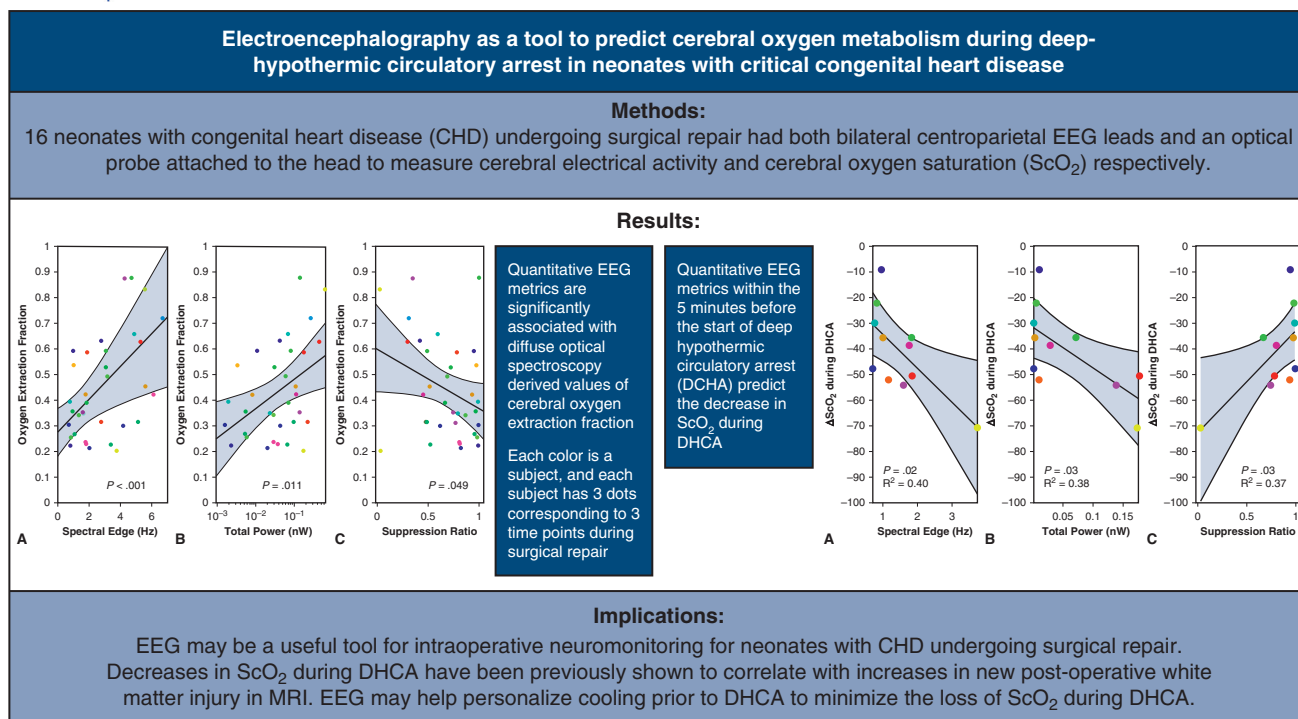
There are several studies that suggest that prolonged time under DHCA is a risk factor for various forms of neurologic injury such as postoperative seizures, new WMI, and neurodevelopmental delays.[4,24,25] There are alternative perfusion strategies to DHCA that are predominant in the current era, but DHCA is still used by a subset of surgeons, and brief periods of DHCA are still sometimes necessary even if not used for the majority of repair.

Study Limitations

A potential confounding variable in the correlation between the end-cooling EEG metrics and the ΔScO_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_2 during DHCA ($P = .09$, $R^2 = .285$). That is, those subjects with longer DHCA times tended to have a greater decrease in cerebral oxygen saturation (ScO_2) 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 by a well-trained epileptologist, in the future, automated EEG algorithms to identify and

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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 (ScO_2) respectively.

Results:

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

Quantitative EEG metrics within the 5 minutes before the start of deep hypothermic circulatory arrest (DCHA) predict the decrease in ScO_2 during DHCA

Each color is a subject, and each subject has 3 dots corresponding to 3 time points during surgical repair

A: P < .001 (Spectral Edge (Hz), Oxygen Extraction Fraction)
B: P = .011 (Total Power (nW), Oxygen Extraction Fraction)
C: P = .049 (Suppression Ratio, Oxygen Extraction Fraction)

A: P = .02, R² = 0.40 (Spectral Edge (Hz), ΔScO₂ during DHCA)
B: P = .03, R² = 0.38 (Total Power (nW), ΔScO₂ during DHCA)
C: P = .03, R² = 0.37 (Suppression Ratio, ΔScO₂ during DHCA)

Implications:
EEG may be a useful tool for intraoperative neuromonitoring for neonates with CHD undergoing surgical repair. Decreases in 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 ScO_2 during DHCA.

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-C, The quantitative EEG metric on the x axis for each scatter plot. A, Spectral edge frequency 95% (Hz). B, TP (nw). C, SR. *EEG*, Electroencephalography; *DHCA*, deep hypothermic circulatory arrest; *ScO₂*, cerebral oxygen saturation; *OEF*, oxygen extraction fraction.

remove artifacts promise to allow clinicians to visualize quantitative EEG metrics in real-time (ie, 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, 1 subject (highlighted in yellow in Figure 3) had a disproportionate influence on the correlation between end-cooling EEG activity and ΔScO_2 during DHCA. This subject's SEF95 immediately before DHCA (SEF95 = 3.74) was more than twice that of the study population's mean (SEF95$_{mean}$ = 1.38). If this subject were to be excluded from the linear regression analyses shown in Figure 3, the relationships between end-cooling SEF95, TP, and SR with ΔScO_2 during DHCA would not be significant (P = .231, P = .13, P = .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 postoperative MRI. Although there are EEG data for 16 subjects, preoperative and postoperative MRI data are available for only 9 subjects (of whom only 7 of 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 postoperative WMI.

CONCLUSIONS

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 CMRO$_2$ 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.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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