Peri-operative amplitude-integrated EEG and neurodevelopment in infants with congenital heart disease

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Congenital heart disease; Pediatrics; Brain; Follow-up studies; Cardiac Surgery

Abbreviations:

aEEG = amplitude-integrated electroencephalography

CHD = congenital heart disease

CPB = cardiopulmonary bypass

ECMO = extra corporeal membrane oxygenation

EEG = electroencephalography

HLHS = hypoplastic left heart syndrome

SWC = sleep wake cycling

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Abstract

Purpose

Peri-operative brain injury is common in young infants undergoing cardiac surgery. We aimed to determine the relationship between peri-operative electrical seizures, the background pattern of amplitude-integrated electroencephalography (aEEG) and two-year neurodevelopmental outcome in young infants undergoing surgery for congenital heart disease.

Methods

150 newborn infants undergoing cardiac surgery underwent aEEG monitoring prior to and during surgery, and for 72 hours post-operatively. Two blinded assessors reviewed the aEEGs for seizure activity and background pattern. Survivors underwent neurodevelopmental outcome assessment using the Bayley Scales of Infant Development (3rd Edition) at two years.

Results

The median age at surgery was seven days (IQR 4-11). Cardiopulmonary bypass was used in 83%. Peri-operative electrical seizures occurred in 30%, of whom ¼ had a clinical correlate, but were not associated with two-year outcome. Recovery to a continuous background occurred at a median 6 (3-13) hours and sleep-wake-cycling recovered at 21 (14-30) hours. Prolonged aEEG recovery was associated with increased mortality and worse neurodevelopmental outcome. Failure of the aEEG to recover to a continuous background by 48 post-operative hours was associated with impairment in all outcome domains ($p<0.05$). Continued abnormal aEEG at seven post-operative days was highly associated with mortality ($p<0.001$).

Conclusions

Peri-operative seizures were common in this cohort of infants but did not impact on two-year neurodevelopmental outcome. Delayed recovery in aEEG background was associated with increased risk of early mortality and worse neurodevelopment. Ongoing monitoring of the survivors is essential to determine the longer-term significance of these findings.

Introduction

Brain injury is a potentially devastating complication of congenital heart disease (CHD) requiring surgery during the newborn period [1, 2]. The developing white matter is particularly vulnerable to acute changes in cerebral perfusion and oxygenation which are typical during the peri-operative period in young infants with complex CHD. Continuous electroencephalography (EEG) provides a real-time picture of the brain's surface electrical activity and therefore offers a time-sensitive method of detecting brain injury.[3]

Amplitude-integrated EEG (aEEG) is used in neonatal intensive care for assessment of seizures and background cerebral activity in high-risk neonates [4-9]. As well as providing real-time continuous bedside monitoring, time-compressed background aEEG patterns have been shown to correlate with magnetic resonance imaging changes [5] and neurodevelopmental outcome in neonatal encephalopathy [7-10]. aEEG has also been studied in infants undergoing extracorporeal membrane oxygenation (ECMO) and in infants after the arterial switch operation [3, 11, 12]. We recently reported an association between adverse outcomes (death or impaired neurodevelopment) and peri-operative aEEG abnormalities in a subgroup of these infants undergoing Norwood-type palliations [13].

Post-operative clinical and electrical seizures, on conventional EEG monitoring, have been shown to correlate with impaired early neurodevelopment in cohorts of young infants before and after cardiac surgery [14-16]. Refinements in perfusion techniques, anaesthetic regimes and surgical approaches, as well as perinatal and post-operative care have together contributed to improved survival in recent years. Thus, the findings of historical studies should only be applied with caution in the current era.

The aims of this study were to ascertain the typical period of aEEG recovery in young infants following a range of cardiac operations, to determine the incidence of peri-operative seizures using continuous 2-channel aEEG before, during and for 72 hours after surgery for CHD and to relate these findings to two-year neurodevelopmental outcome.

Patients and Methods

Participants

Between 2005 and 2008, 150 full-term infants scheduled to undergo surgery for CHD before 2 months of age, were enrolled into a prospective study of brain injury in CHD, at The Royal Children's Hospital, Melbourne (Centre 1) and Starship Children's Hospital, Auckland (Centre 2). Infants were excluded for the following reasons: 1) gestational age of <36 weeks; 2) a genetic abnormality independently associated with impaired neurodevelopment; or 3) the need for pre-operative ECMO. The study was approved by both hospitals' Human Research and Ethics Committees and parents of participants consented to their inclusion.

Amplitude-integrated EEG

aEEG monitoring was performed on each participant using the BRM2 cerebral monitor (BrainZ Instruments, Auckland, New Zealand). A two-channel recording of electrical activity was collected from scalp electrodes positioned in the C3, P3, C4, P4 positions of the international 10-20 EEG system. The monitor used a computer generated algorithm to filter and compress raw data for each cerebral hemisphere. Data were considered acceptable for analysis according to the following criteria: impedance of less than 10k Ω , absence of movement or electrocardiographic artefact on the raw trace, and absence of interference from diathermy or other electrical devices.

A neonatologist experienced in aEEG interpretation, and blinded to clinical information, analysed all de-identified aEEG recordings offline. The complete compressed background recording and the intra-operative raw trace were assessed. Background traces were classified according to the dominant pattern at the following pre-defined phases:

Phase 1 – One hour pre-operative aEEG.

Phase 2 – Intra-operative aEEG: a) from commencement of anaesthesia; b) during cooling and maintenance of the target hypothermic temperature; c) during rewarming and d) after cardiopulmonary bypass (CPB) until surgery was completed (or from the time normothermia was reached if CPB not used).

Phase 3 – Post-operative aEEG: hourly for six hours then six hourly until 72 hours after the cessation of CPB (or one hour post-CPB when CPB was not utilised).

Phase 4 – One hour late post-operative aEEG seven days following surgery.

Background aEEG activity was classified as continuous (normal), discontinuous or suppressed (burst suppression, low voltage or flat trace), based on a previously described system.[5, 17] The time taken for the aEEG to ‘recover’ to continuous background activity (regardless of sleep-wake-cycling (SWC)) and to SWC were documented for each patient (up to 72 post-operative hours). This was then classified as normal (continuous) or abnormal at 48 hours. Seizures were defined as repetitive waveforms evolving over a minimum of ten seconds on either hemisphere. Suspected seizures on the amplitude-integrated component were confirmed on the raw EEG and considered by a second blinded assessor. Seizures identified acutely were managed at the discretion of the treating clinical team. A seizure detection algorithm was not utilised.

Operative Management

Anaesthetic management followed institutional cardiac anaesthesia protocols, with high-dose fentanyl, inhaled isoflurane and muscle relaxants. Benzodiazepines or barbiturates were not administered during surgery. For the infants undergoing CPB, the perfusion strategy included continuous full-flow CPB at 150mL/kg/min with a procedure-specific target temperature during CPB of 22-34°C. Alpha-stat acid-base management was utilised in both centres, with the use of pH-stat at temperatures below 30°C in Centre 2. Antegrade cerebral perfusion (ACP) was maintained via a Goretex shunt to the innominate artery in all infants undergoing Norwood-type reconstructions, and infants with biventricular circulations requiring arch reconstruction in Centre 1. ACP was maintained at flows of 30-40% of 'full' CPB flow, with flow adjusted to target a right radial arterial mean pressure of 30-45 mmHg. Brief periods of deep hypothermic circulatory arrest (DHCA) were used in Centre 2 (but not Centre 1) with biventricular circulation during arch reconstruction, and during surgery to the atrial septum. Continuous haemofiltration was used in all patients during CPB, with a target haematocrit of greater than 30% during CPB, and 40-45% at the completion of CPB.

There were no other differences in peri-operative management between centres. Following selected operations, including the Norwood procedure, the sternum was left open with the intention of delayed closure after a period of haemodynamic stability. Post-operative analgesia and sedation were achieved with continuous infusions of morphine (10-40mcg/kg/hr) and midazolam (1-3mcg/kg/min).

Neurodevelopmental Assessment

Survivors underwent a neurodevelopmental assessment by a paediatrician and/or psychologist at two years, using the Bayley Scales of Infant Development (3rd Edition) (BSID-3) for which the normative mean equates to a score of 100 ± 15 . Severe neurodevelopmental delay for a given

domain (cognitive, language or motor) was defined as a score more than two standard deviations (SD) below the normative mean (<70).

Statistical analysis

Data were analysed using descriptive statistics. Parametric and non-parametric data are reported using mean $\pm$ SD or median (interquartile range) respectively. aEEG background recovery was analysed as both a continuous variable and dichotomous variable (recovery to a continuous background by 48 hours). Categorical variables were analysed using a χ^2 test. T-tests, Wilcoxon rank-sum tests and linear regression were used for analysis of continuous variables. Statistical significance was determined at a p-value of <0.05.

Results

Table 1 shows demographic and surgical details of the study participants. Participants were divided into four pre-operative categories, according to a previously described classification [18], as follows: two ventricle without aortic arch obstruction (such as transposition of the great arteries) 57 (38%); single ventricle with aortic arch obstruction (such as hypoplastic left heart syndrome (HLHS)) 41 (27%); single ventricle without aortic arch obstruction (such as pulmonary atresia) 28 (19%); two ventricle with aortic arch obstruction (such as coarctation) 24 (16%).

Two-year neurodevelopment

Twenty (13%) participants died before two years, at a median 55 days (IQR 27-61), eight prior to hospital discharge. Five (4%) were lost to follow-up and 125 children (96% of survivors) underwent neurodevelopmental evaluation. Mean cognitive composite scores were 93.2 ± 13.7 and five (4%) children had severe cognitive delay (score <70). Mean language scores were 93.5

± 16.2 and ten (8%) children had severe language delay. Mean motor scores were 96.7 ± 12.7 and two (2%) children had severe motor delay. Mean scores were significantly lower than the normative mean in all domains (cognitive and language $p < 0.0001$; motor $p = 0.01$).

Seizures

Peri-operative electrical seizures were identified in 43 (30%) infants, seven of whom had clinical signs and were treated with anticonvulsants. There was 100% agreement between assessors regarding the presence of electrical seizures. Pre-operative seizures occurred in four (3%) infants and intra-operative seizures [Figure 1] occurred in 20 (13%), most commonly during the hypothermic or rewarming phase of CPB. During the post-operative recovery period, 27 (19%) infants displayed electrical seizures and a further three (2%) had seizure activity on the late post-operative aEEG. Minimum core temperature did not vary between those with or without intra-operative seizures and there was no relationship between the use of CPB or circulatory arrest and the occurrence of peri-operative seizures ($p > 0.2$). There was also no relationship found between the occurrence of peri-operative seizures and diagnostic group [Table 2], mortality or developmental scores ($p > 0.10$).

aEEG Background

Figure 2 shows the background aEEG characteristics at each phase. No relationship was found between pre-operative background and two-year outcome. At or below 28°C all intra-operative background traces had either isoelectric or low voltage activity [Figure 1B]. There was considerable variability in the degree of background suppression $> 28^{\circ}\text{C}$. Recovery to a continuous aEEG background occurred within 24 hours in 112 participants (77%), by 48 hours in 118 (81%) and by 72 hours in 130 (90%). Amongst the 130 infants whose background patterns had recovered within 72 hours, the median recovery time was 6 (3-13) hours. SWC was

established by 72 hours in 118 infants at a median 21 (14-30) hours. Intra-operative seizures were associated with a 10.6 [95%CI 1.1, 20.1] hour delay in aEEG recovery to a continuous background (p=0.03) but not to return of SWC (p=0.46). Post-operative seizures did not impact on the recovery time of the background activity.

Prolonged recovery to a continuous background was associated with lower mean cognitive scores (Coeff 0.14 [95%CI 0.01, 0.28]; p=0.03) and motor scores (Coeff 0.17 [95%CI 0.05, 0.30]; p=0.008) [Table 3]. Delayed recovery of SWC was associated with lower cognitive scores (Coeff 0.17 [95%CI 0.05, 0.28]; p=0.006). Participants with a cognitive or language score <70 had mean recovery times to continuous background which were 16.6[95%CI 0.5, 32.8] hours (p=0.04) and 14.8 [95%CI 3.2, 26.3] hours (p=0.01) longer than those with a score within two SDs of the normative mean. Likewise, recovery to normal SWC was 32.5 [95%CI 14.0, 30.9] hours, 14.5 [95%CI 0.8, 28.3] hours and 42.8 [95%CI 13.6, 72.1] hours later in those who subsequently had respective cognitive (p=0.007), language (p=0.04), or motor (p=0.004) scores <70. Death before two years was associated with a 19.4 [95%CI 9.3, 29.0] hour increase in post-operative recovery time to a continuous background compared with survivors (p=0.0001) and a 14.8 [95%CI 4.3, 25.3] hour increase in time to return of SWC (p=0.006).

Post-operative ECMO was associated with delayed aEEG recovery – 50% of those on ECMO failed to recover background aEEG by 48 hours compared with 10% of those without ECMO ($\chi^2=12.8$, p<0.0001). Seven of the 11 children who had required ECMO died and one declined follow-up. Removal of the remaining three children from outcome analysis did not alter the impact of delayed aEEG recovery on outcome. Eight infants had persisting discontinuous or low voltage background patterns one week after surgery, of whom five had required ECMO and subsequently died ($\chi^2=16.4$, p<0.001).

Time of recovery to a continuous background was longer in those with single ventricle physiology (with either obstruction to the systemic or pulmonary circulation) compared to those with two ventricle physiology pre-operatively ($p=0.0002$) [Table 2], but there was no significant prolongation of recovery time specifically related to delayed chest closure ($p=0.051$). Mean cognitive ($p=0.028$) and motor ($p=0.002$) scores were also lower in those with single ventricle physiology and 80% of the deaths occurred in this group. However, time to return of SWC was not related to pre-operative cardiac anatomy ($p=0.20$).

Discussion

This is the first cohort study to report on peri-operative aEEG monitoring across a range of congenital heart lesions. Moreover, this is the first study which links post-operative aEEG recovery with neurodevelopmental performance in this population. Sub-clinical peri-operative seizures were common during the peri-operative period, but these were not related to two-year outcome. However, post-operative aEEG recovery time was related both to impaired neurodevelopment and increased mortality.

Seizures

Peri-operative seizures were observed in 30% of our cohort. Pre-operative epileptiform activity may have been underestimated compared with a previous study which included a more prolonged pre-operative recording period and detected seizures in 19% of infants [19]. Intra-operative seizures were observed in 13%. This phenomenon has been reported as rare during adult cardiac surgery, but has rarely been studied in infants [20]. In the Boston Circulatory Arrest study, conventional multi-channel EEG recording continued during surgery, and intra-operative seizures were not observed. However perfusion strategies in that cohort included hypothermia to

$\leq 18^{\circ}\text{C}$ in all patients, and anaesthetic management included routine administration of thiopentone at the nadir of body temperature (10mg/kg), which could suppress intra-operative electrical activity.

Post-operative electrical seizures were identified in 19% of our participants. Similar rates of electrical seizures have been reported in other post-operative cohorts including clinical seizure rates of 16-17% after surgery for HLHS [21-24]. Immature brains are less likely to exhibit clinical manifestations of seizures despite their increased frequency [25]. This reflects the typical ‘uncoupling’ of clinical and electrical seizures commonly seen in neonates, which are further masked by pharmacotherapy [26]. Andropoulos *et al.* recently reported post-operative seizures in only 3% of neonates undergoing single ventricle palliation, but all patients in that sample had received intravenous midazolam throughout their surgery as well as boluses during their post-operative recovery [27]. Though this may have increased the seizure threshold, it will be essential to determine whether this difference in seizure occurrence translates into improved outcomes. While in the Boston cohort, post-operative electrical seizures were associated with impaired neurodevelopment at one, four and 16 years of age, but not at eight years [15, 28, 29], we did not demonstrate a relationship at two years of age using the BSID-3 assessment.

Post-operative aEEG

Failure of the aEEG background to recover to a continuous pattern within 48 hours after CPB was highly correlated with increased mortality and worse two-year neurodevelopment in survivors. There is limited literature regarding EEG recovery in infants after cardiac surgery. In the Boston cohort, background EEG had not yet returned to baseline at 48 hours in the study participants, which may reflect a difference in anaesthetic and post-operative strategies. In a cohort of infants followed up after the arterial switch operation, there was a wide variability in

time to recovery of background aEEG and 18/20 participants had normal neurodevelopment at 30 months [3]. We have previously reported an association between delayed post-operative aEEG recovery and motor delay in a sub-group of these infants undergoing the Norwood procedure [30]. Correlation between aEEG and neurodevelopmental outcome has not previously been reported in broader cohorts of infants with CHD. Importantly, our findings are consistent with studies of neonatal encephalopathy, in which time to recovery of aEEG background, and return of SWC, is correlated with outcome [7, 31]. These data suggest that post-operative aEEG monitoring may have a role to play in identifying children at higher risk of a poor outcome.

The finding that aEEG background, but not seizures, was related to neurodevelopmental impairment may reflect the accuracy of a two-channel tool designed to examine background patterns rather than seizures. It may also reflect the nature of cerebral injury in this population, namely the dominance of white matter injury rather than localized cortical injury, which is more likely to present with seizures.

Limitations

The first, and probably most important limitation to our study, relates to our modality of cerebral monitoring. We applied two-channel aEEG during the study, and did not have access to continuous conventional multichannel EEG monitoring for the extensive period of monitoring. In terms of seizure identification, while it is possible that the aEEG may have missed occasional seizures, particularly pertaining to the frontal regions, it is generally accepted that there is good correlation between the two methods when interpreted by experienced clinicians [32, 33]. The investigator assigned to interpretation of the aEEG was experienced in this, having been trained by colleagues who have extensively published in the field [34-37]. Seizures may also have been

missed in the phase 1 and 4 components of recording due to the short time period over which monitoring was applied at these points.

Less evidence is available regarding the accuracy of aEEG in interpretation of the background activity in infants after heart surgery. Clancy *et al.* described good correlation between single channel aEEG and conventional multi-lead EEG at the two extreme categories (normal and markedly abnormal) but significantly weaker correlation in the intermediate categories [38].

Those investigators used single channel aEEG, and did not have access to ‘raw’ aEEG traces and the authors acknowledged that the agreement between the two modalities could be enhanced with two-channel recording [39], examination of the raw trace (particularly with an experienced aEEG reader) and interpretation of background patterns according to the Hellstrom-Westas classification [17]. All of these potential factors were used or incorporated in our study.

A second limitation relates to the potential contribution of sedative and analgesic drugs to the interpretation of aEEG. While it is generally believed that these agents are thought to suppress aEEG background activity, there is little published evidence to support this, particularly in full-term neonates without significant acute diffuse brain injury, or refractory seizures [40]. All infants in our study received weaning doses of morphine and midazolam during the post-operative period, which could influence aEEG recovery, particularly as the sickest infants are more likely to require longer periods of such agents. However, in a subgroup of this cohort, we found no relationship between post-operative aEEG background pattern and infusions of morphine or midazolam [41]. All infants in this study received similar anaesthetic regimens, but there remains the potential for effects on the aEEG of agents such as fentanyl and isoflurane, which require further elucidation.

Finally, inclusion of a control group with this cohort would have strengthened the assessment of neurodevelopmental impact on these children. Previous assessments of cardiac children have not incorporated the BSID-3 which may overestimate abilities compared with previous versions of the test [42].

Conclusions

Electrical seizures are common in young infants undergoing surgery for CHD, both during and after surgery, but do not predict two-year neurodevelopmental outcomes. A prolonged aEEG recovery phase after surgery is associated with both increased mortality and impaired neurodevelopment in all domains at two years of age in survivors. Peri-operative neuromonitoring is essential in these high risk infants. Further follow-up will determine the longer-term significance of these findings.

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Table 1. Demographic and surgical details of included participants (n=150).

Male	95 (63%)
Birth weight (kg)	3.3 ± 0.5
Head circumference (cm)	34.5 ± 1.8
Gestational age at birth (weeks)	39 ± 1.6
Age at surgery (days)	7 (4-11)
Cardiopulmonary bypass used	125 (83%)
Duration of CPB (minutes)	184 ± 60
Minimum esophageal temperature during bypass (°C)	24.5 ± 5.3
Aortic cross-clamp time (minutes)	94 ± 40
Circulatory arrest	47 (31%)
Duration of circulatory arrest (minutes)	8 (5-17)
Antegrade cerebral perfusion	48 (32%)
Immediate post-operative lactate (mmol/L)	3.4 (2.0-4.8)
Post-operative ECMO	11 (7%)

Number (%), mean ± standard deviation or median (interquartile range) are reported.

Table 2. Relationship between cardiac category and occurrence of electrical seizures and median aEEG recovery time.

Pre-operative category	Any seizures †	Intra-operative seizures	Post-operative seizures	Median (IQR) recovery time to continuous background (hours) *
Single ventricle	6 (22%)	1 (4%)	3 (11%)	10 (4-20)
Two-ventricle	15 (27%)	6 (12%)	10 (18%)	4 (2-11)
Single ventricle with aortic arch obstruction	13 (33%)	9 (23%)	7 (18%)	16 (4-45)
Two-ventricle with aortic arch obstruction	9 (41%)	4 (18%)	7 (32%)	4 (2-13)
Total	43 (30%)	20 (13%)	27 (19%)	8 (3-18)

* Infants whose aEEG had not recovered by the end of the recording were underestimated to have recovered by 72 hours.

† Some infants had seizures within more than one epoch.

Table 3. Impact of delay in recovery of aEEG beyond 48 hours post-operatively on two-year outcome.

Two-year outcome	aEEG recovery by 48	Abnormal aEEG at 48	p-value
	hours post-CPB	hours post-CPB	
Mean cognitive score	94.3 [95%CI 91.8, 96.8]	83.5 [95%CI 72.2, 94.8]	0.017
Cognitive score <70	3/111 (3%)	2/10 (20%)	0.008
Mean language score	94.3 [95%CI 91.3, 97.4]	81.3 [95%CI 70.9, 91.7]	0.016
Language score <70	7/111 (6%)	3/10 (30%)	0.009
Mean motor score	97.7 [95%CI 95.4, 100.1]	85.9 [95%CI 75.6, 96.2]	0.005
Motor score <70	1/111 (1%)	1/10 (10%)	0.031
Two year mortality	12/126 (10%)	8/19 (42%)	<0.001
Post-operative ECMO	5/121 (4%)	5/19 (26%)	<0.001

Figure 1. Intra-operative aEEG. Ten seconds of raw trace for each hemisphere (top two traces); and the time-compressed aEEG trace (bottom two traces) over five hours. A) Anesthetic induction and commencement of surgery; B) cooling and maintenance of hypothermia (complete suppression of the background trace); C) rewarming and cessation of CPB; D) conclusion of surgery. Electrical seizure (orange arrow highlighting correlation between aEEG and raw trace) occurring during rewarming following CPB and circulatory arrest.

Figure 2. Predominant background aEEG pattern at each phase of recording. The reduction in data available for all recording phase, especially during surgery (Phase 2), is related to artefact-affected or missing intraoperative data.