Review article

Perioperative electroencephalography in cardiac surgery with hypothermic circulatory arrest: a narrative review

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VISUAL ABSTRACT

Key question: What is the role of perioperative electroencephalography (EEG) in cardiac surgery with hypothermic circulatory arrest?

Key findings: EEG is used to guide arrest strategy and detect brain injury but there is limited evidence of direct benefit on outcome

Take-home message: No prospective studies compare EEG- vs no EEG-monitoring. More studies investigating EEG-based interventions during HCA surgery are required

ABSTRACT

Objectives: Cardiac surgery with hypothermic circulatory arrest is associated with neurological morbidity of variable severity and electroencephalography is a sensitive proxy measure of brain injury. We conducted a narrative review of the literature to evaluate the role of perioperative electroencephalography monitoring in cardiac surgery involving hypothermic circulatory arrest.

Methods: MEDLINE, EMBASE, CENTRAL and LILACS databases were searched to identify studies utilising perioperative electroencephalography during surgery with hypothermic circulatory arrest in all age groups, published since 1985 in any language. We aimed to compare electroencephalography use with no use but due to the lack of comparative studies, we performed a narrative review of its utility. Two or more reviewers independently screened studies for eligibility and extracted data.

Results: 40 single-centre studies with a total of 3,287 patients undergoing surgery were identified. Most were observational cohort studies (34, 85%) with only one directly comparing electroencephalography use with no use. Electroencephalography continuity (18, 45%), seizures (15, 38%), and electrocerebral inactivity prior to circulatory arrest (15, 38%) were used to detect, monitor, prevent, and prognose neurological injury. Neurological dysfunction was reported in almost all studies and occurred in 0-21% of patients. However, the heterogeneity of reported clinical and electroencephalography outcome measures prevented meta-analysis.

Conclusions: Electroencephalography is used to detect cortical ischaemia, seizures, predict neurological abnormalities and may guide intraoperative cerebral protection. However, there is a lack of comparative data demonstrating benefit of perioperative electroencephalography monitoring. Use of a standardised methodology for performing electroencephalography and reporting outcome metrics would facilitate the conduct of high-quality clinical trials.

Abstract word count: 250

Keywords: Review; Paediatric cardiac surgery; Electroencephalography; Neuroprotection; Hypothermic circulatory arrest; Neurological injury.

ABBREVIATIONS

CPB	Cardiopulmonary Bypass
DHCA	Deep Hypothermic Circulatory Arrest
ECI	Electrocerebral Inactivity
EEG	Electroencephalography
HCA	Hypothermic Circulatory Arrest
RCT	Randomised Controlled Trial
SACP	Selective Antegrade Cerebral Perfusion

INTRODUCTION

Hypothermia remains an essential technique to protect the brain during cardiac surgical procedures which require circulatory arrest [1]. As core temperature decreases, cerebral metabolism is reduced thereby offering a window of neuroprotection, with lower core temperatures targeted for more complex and extensive repairs that require prolonged arrest. Despite the use of hypothermia in conjunction with cerebral perfusion techniques, neuromonitoring, and neuroprotective drug regimes, new postoperative neurologic deficits can still occur in both adults and children undergoing cardiac surgery, and the reason for this is not completely understood [2,3].

Electroencephalography (EEG) records the summated postsynaptic potentials of neural tissue from electrodes placed on the scalp [4]. This activity is classified as normal or abnormal based on its location, morphology, and amplitude relative to the age of the patient. EEG can be used to detect seizures, signs of ischaemia, and guide the depth of anaesthesia and hypothermia [5,6]. In spite of its wide availability in clinical centres, perioperative EEG monitoring is not routinely used during cardiac surgery with hypothermic circulatory arrest (HCA). A recent survey on its use during aortic arch surgery suggested that it is only performed routinely in approximately 17% of European centres [7]. Guidelines from the American Society of Neurophysiological Monitoring consider EEG in cardiac surgery with cardiopulmonary bypass (CPB) to be a practice option rather than a standard of care, as there are no standards for patient management or established role in improving outcomes [8]. We therefore conducted a narrative review of studies reporting EEG technique and/or outcomes of perioperative EEG monitoring in children and adults undergoing cardiac surgery with HCA to evaluate whether there was consistency in methodology, synthesise the current evidence-base, and identify any impact on postoperative outcomes.

MATERIALS AND METHODS

This review was conducted with reference to the Cochrane handbook for reviews of interventions [9] and reported in accordance with the PRISMA statement [10]. All eligibility criteria, search terms and data items were prespecified, and the review was prospectively registered on PROSPERO (CRD42021247700) (https://www.crd.york.ac.uk/prospero).

Study eligibility

We included patients of all ages undergoing cardiac surgery with HCA. We identified studies assessing perioperative EEG monitoring (processed or unprocessed) and whether the study compared the use of EEG monitoring with no EEG monitoring. Outcomes of interest were neurological status which encompassed any observer-reported outcome indicating neurological dysfunction, and perioperative EEG technique. We included all randomised controlled trials (RCTs), non-randomised trials, prospective and retrospective observational cohorts, case-series, and cross-sectional studies published in any language since 1985, so that retrieved articles better reflected current perioperative management.

Cardiac surgery was defined as any therapeutic clinical procedure performed on the heart or great vessels and HCA as cessation of the circulation following systemic cooling via CPB. EEG was defined as the subjective or quantitative interpretation of cortical activity recorded from at least two electrodes placed on the scalp.

Secondary publications, sub-studies, or long-term outcomes of previously reported studies were excluded unless the results were specifically related to the utility of EEG monitoring or reported additional neurological outcome measures. Studies published only as a conference abstract, or for which all options to obtain the full text were exhausted were excluded due to insufficient data.

Search strategy

We searched international primary research databases (MEDLINE, EMBASE, CENTRAL, LILACS) from 1st January 1985 to 13th May 2022 and reference lists of relevant articles, systematic reviews, and meta-analyses to identify all eligible studies. The search terms used were comprehensive and adapted for each database, with database-specific filters to identify the population and intervention of interest (see Supplementary material).

Study selection and data extraction

Title and abstracts, then full-text publications of all identified articles were screened independently by two reviewers (WM and TG) to generate a database of included studies. Data were extracted independently by two reviewers (two of WM, TG and ND) from the full text and any published protocols or supplemental material; a full list of data items and descriptors is available in the Supplementary material. Non-English articles were translated and any disagreements on study selection or data extraction were resolved by consensus.

Statistical analysis

Continuous data were expressed as median with interquartile range (IQR), mean with standard deviation (SD), or range. Categorical data were expressed as counts and percentages where relevant. We did not plan to perform a meta-analysis or analyse sensitivity and homogeneity because we did not anticipate retrieving homogenous studies relatively resistant to bias. In the event of no or limited studies comparing EEG monitoring with no EEG monitoring, we planned to undertake a narrative review of studies describing perioperative EEG monitoring.

RESULTS

From 341 unique records, we identified 40 studies with a description of perioperative EEG monitoring that included 3,287 patients undergoing cardiac surgery with HCA. Only one study directly compared detailed outcomes between groups with perioperative EEG monitoring versus no monitoring. We therefore performed a narrative review of the non-comparative studies, and one comparative study, on the utility of perioperative EEG monitoring (figure 1).

Included studies

EEG monitoring was performed intraoperatively only (19, 48%, n=2,245) [13-31], postoperatively only (2, 5%, n=283) [6,32], or a combination of pre-, intra- and/or postoperatively (19, 48%, n=759) [33-51]. Thirty nine (98%, n=3,276) studies reported a combination of clinical and EEG outcomes of interest, the other (n=11) focussed solely on EEG analysis technique [29].

All studies were single centre, consisting of six (15%) reports of RCTs, three of which were sub-studies that provided additional outcome data [44,45,50], 18 (45%) retrospective cohort studies, and 16 (40%) prospective cohort studies, three of which were sub-studies that provided additional data [24,41,49] (table 1 and supplementary material).

Most (20, 50%) studies focussed on adult patients, originated from the USA (28, 70%), and most often involved surgery to the proximal aorta or aortic arch (17, 43%). Almost all were published in English (38, 95%), most often in specialist cardiothoracic surgery journals (13, 33%). The number of participants per study ranged between 6 and 791 (median 46, IQR: 20-109).

Outcome measures

The most commonly reported clinical outcome measure was postoperative neurological dysfunction, which occurred in 0-21% of patients. This broad term encompassed neurological signs and symptoms ranging from confusion to paralysis. When measuring clinical outcome, a variety of methods were used, including recognised clinical examinations (Glasgow Coma Scale, neurologic exam) and imaging (ultrasound, computed tomography, magnetic resonance imaging). Outcome measures were typically assessed before hospital discharge. Only 6 (15%) studies used scales to assess long-term neurodevelopmental outcome, exclusively in children [41,43,45,46,48,49] (as shown in the supplementary material). The majority of these studies identified that both the presence of seizures and increasing duration of ECI on EEG were associated with poor neurodevelopmental outcomes.

The most common EEG outcome measure reported was an assessment of EEG continuity during cooling and rewarming (18, 45%), which was used to predict postoperative outcome, assess anaesthetic depth, and guide HCA strategy [13,15–18,20,22,24,26,27,29,34–36,39,43,47,48]. Of these, three (17%) studies report longer durations of non-continuous EEG following HCA associated with postoperative neurological dysfunction [13,24,41], and in three there was a trend that was either not significant or not associated with outcome [18,27,48]. EEG was used for seizure detection, or to predict seizure occurrence in 15 (38%) studies [6,18,28,32–36,38,40,42–44, 48, 51]. Seizures occurred in 0-21% of cases, of which up to 85-100% were subclinical (i.e., only detectable by EEG). The presence or duration of electrocerebral inactivity (ECI) on EEG prior to deep HCA (DHCA) was used in 15 (38%) studies as an indicator of optimised cerebral protection and to guide HCA strategy [13,14,16–19,21,23,25,27,29,30,39–41]. Of these, 14 involved adults and one was exclusively in neonates [41]. With the exception of seizure monitoring, 11 (28%) studies utilised EEG to detect background abnormalities indicative of neurological injury [31,35–37,40,42,43,46,48,50,51], and the rate of EEG abnormalities detected varied between 0-44%.

One retrospective study directly compared clinical outcome in patients undergoing perioperative EEG monitoring against a control group [31]. They identified early detection of stroke (75% sensitivity) and accurate prediction of no stroke (97% negative predictive value) using a neuromonitoring protocol that included EEG. A single-centre study reported outcomes of aortic arch surgery using EEG-guided DHCA [18] and compared outcomes to their previously reported cohort [52]. They identified a lower incidence of mortality, stroke, and reoperation for bleeding in the more recent study and report the only difference between the cohorts was the use of ECI-guided DHCA.

Other infrequently reported EEG parameters included changes in the amplitude or frequency of cortical activity to detect intraoperative ischaemia in four(10%) studies [15,21,22,31]. When detected, this resulted in; a change in cannulation strategy; the depth of hypothermia prior to circulatory arrest or the cardiopulmonary bypass (CPB)/cerebral perfusion pump flow/blood pressure augmentation; postoperative imaging and catheter-based interventions. A retrospective study of aortic arch procedures identified asymmetries in EEG activity between left and right hemispheres following innominate artery cannulation, reflecting uneven active cooling of the brain [36].

The interpretation of EEG activity in relation to ECI was often defined as cortical activity less than 2μV for 2-3 minutes. Whilst national and international guidelines for EEG interpretation are widely available [8,53–59], few explicitly cited these standards. The number of electrodes used to record the EEG varied between 2 and 21, with 15 (38%) utilising the full international 10-20 scalp positions [53] followed by a limited montage consisting of between 2 and 12 electrodes (13, 33%). These studies frequently cited the 10:20 system for electrode application but few reported recording parameters such as filter settings (6, 15%) and EEG sampling rate (4, 10%). Seventeen (43%) studies provided limited or no information on the technical standards of EEG recording.

DISCUSSION

Perioperative EEG during cardiac surgery with HCA is used: to detect neurological abnormalities, seizures, and ischaemia; to guide the depth of anaesthesia and hypothermia before arrest; and to predict clinical outcome. However, we found no prospective studies comparing perioperative EEG monitoring versus no EEG monitoring in adults and children undergoing cardiac surgery.

In the 40 articles included in this review, there were only three RCTs, none of which used EEG monitoring as the primary intervention. The remaining prospective and retrospective cohort studies demonstrated heterogeneity in the interventions used and outcome measures reported. Almost all lacked a control group of patients who were not monitored with perioperative EEG, limiting our evaluation of the role of EEG in improving postoperative outcomes. As a result, this review provides limited evidence to support EEG monitoring during HCA surgery, a technique which is used in some centres to guide surgical decision making.

Seizures

Perioperative seizures (which occurred in up to 21% of patients) and the cumulative burden of seizures are associated with unfavourable neurological outcomes in children [60] and adults [61] following admission to intensive care. In our review, a high proportion of seizures in the perioperative period were only detected by EEG. It would therefore seem appropriate to utilise EEG to detect these events, as recommended by guidelines for continuous EEG monitoring in neonates [54].

EEG Continuity

Monitoring EEG continuity during cooling, HCA, and rewarming could indicate whether a relationship exists between the depth/rate of hypothermia, rate of rewarming, and postoperative morbidity. As cooling progresses, periodic complexes intermix with background EEG activity, and the amplitude of cortical activity decreases, becoming separated by ever increasing periods of relative electrical suppression (i.e. a burst-suppression pattern) until ECI is achieved; the reverse occurs with rewarming [23,24,30,39]. The time and temperature at which these milestones occur is highly variable between patients and thus cannot be accurately predicted by other clinical metrics [19]. If the timing and duration of ECI is associated with neurological outcome, this would support the utility of EEG as an intraoperative neuroprotection tool to ensure ECI has been obtained prior to DHCA.

EEG Utility

In this review, postoperative neurologic dysfunction was associated with prolonged time to the return of continuous EEG activity [13, 24] and longer periods of ECI, in select studies [41]. One study reviewed stroke rates in 364 adults who required aortic arch repair with HCA [31]. Of these, 223 were monitored with evoked potentials (EPs) and EEG. Surgeons were alerted when specific EP/EEG monitoring criteria were breached. Twelve developed early stroke, which was detected using EPs (9/12) and EEG (1/12). Although there were no significant differences in stroke rate between monitored and unmonitored groups; intraoperative detection of stroke in the monitored group led to earlier intervention which may have limited brain injury. Authors provide a summary of stroke detection and intervention criteria; however, EEG-criteria breaches were infrequent, limiting the EEG monitoring evidence-base.

No study reported an association between outcome and the rate and depth of cooling before DHCA. This has been shown to affect synaptic activity in animal studies, with higher rates of cooling causing a progressive decrease in activity and lower rates promoting the preservation of activity and tissue plasticity [62]. Fast rewarming can cause brain injury in both animal [63] and human studies [64]. This may explain some of the variation seen in the time to achieve ECI and return of continuous EEG activity, although many other factors including anaesthetic regime may contribute to this finding.

As moderate hypothermia is being slowly introduced in surgical practice, the role of EEG could move from ensuring ECI prior to circulatory arrest to preserving some degree of continuity in EEG activity. In a recent series, EEG monitoring was used during hemiarch replacement with moderate HCA and selective antegrade cerebral perfusion (SACP) [15]. Immediately after circulatory arrest, ECI occurred in 45% of patients, which was indicative of cerebral ischaemia. EEG activity was re-established following SACP in all but two cases; in one, asymmetric activity was restored following bilateral ACP, and in the other CPB was re-established and the depth of hypothermia increased before circulatory arrest. They concluded that intraoperative EEG may have specific value in identifying patients with persistent cerebral ischaemia, even after SACP.

Role of EEG in perioperative monitoring

The EACTS/ESVS 2019 expert consensus document on the management of thoracic aortic and aortic arch disease identified widespread use of perioperative EEG monitoring but a lack of evidence for an incremental benefit [65]. Similarly, a systematic review and meta-analysis on outcomes in children following DHCA with EEG monitoring identified 19 studies published in English since 1990 [66]. They reported similar pooled event rates of clinical seizures (12.9%), EEG seizures (14.9%), neurological abnormalities (29.8%) and EEG abnormalities (17.3%) to our findings in adults and children. They concluded that despite its frequent use EEG remains poorly studied.

To facilitate the synthesis of findings from multiple studies, valid and comparable outcome measures must be reported [67]. We found variation in the utilisation, acquisition and recording period of EEG, with inconsistent use of measures to evaluate the same outcome. EEG continuity, seizure, and ECI monitoring were the most commonly used metrics but not all mention how EEG patterns and seizures were classified. Similarly, metrics of neurological dysfunction were the most commonly reported clinical outcome measure, but signs and symptoms used to define this were broad, ranging from confusion to paralysis, and measurements were performed at variable time points. This disparity reflects the absence of a standardised method for reporting perioperative EEG, and measurement of clinical outcomes following cardiac surgery.

Long-term assessment of neurological outcomes following surgery with HCA represents the gold standard to detect more subtle yet persistent neurological deficits, but these were infrequently performed, perhaps due to the burden it places on participants and researchers. In addition, those who require surgery with HCA typically have a multitude of pre-existing comorbidities, heterogeneous and complex heart disease, and variability in the length of postoperative hospital stay; measures used to define neurological outcomes during early childhood are also dependent on age. These factors make it inherently difficult to attribute postoperative injury to any one factor and challenging to compare the neonatal, child, and adult populations. Other than for the detection of postoperative seizures, there is currently limited evidence supporting EEG metrics, such as disappearance/return of EEG continuity, or the time and duration of ECI in guiding perioperative care. In studies that monitored ECI attainment before DHCA, a consistent definition of ECI, and how long it needs to be established before circulatory arrest is required.

Limitations

The limitations of this review include: the lack of RCTs directly comparing the use of EEG monitoring with a control group; our inability to perform a meta-analysis due to the lack of comparable outcome measures; and a risk of reporting bias, although minimised by performing an extensive search across multiple databases and including non-English language articles.

Conclusions

Perioperative EEG monitoring in cardiac surgery with HCA can detect seizures and neurological abnormalities, identify intraoperative ischaemia, and may guide cerebral protection and predict outcome. However, the inconsistent metrics used to record, acquire, and interpret EEG, and clinical outcome measures limit the evidence base to inform clinical practice. No prospective studies compared perioperative EEG versus no perioperative EEG monitoring and thus there is a lack of direct evidence to demonstrate whether EEG monitoring may have a role in improving clinical outcomes. An assessment of EEG continuity during HCA could provide insight into improving perioperative cerebral protection. A standardised approach to EEG monitoring during HCA and postoperative clinical outcome reporting is required to inform the design of future clinical trials.

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Conflict of interest: None declared.

Figure legend

Central Image: EEG burst-suppression before electrocerebral inactivity in hypothermic circulatory arrest surgery.

Figure 1. PRISMA flow diagram of study selection. EEG: Electroencephalography.

Data availability statement: The data underlying this article are available in the article and in its online supplementary material.

Table 1. Summary characteristics of included studies.

Lead Author	Year	Country	Study type	n	Age	Condition	HCA		EEG	
							Guide	End point	When used	Outcome measure/ Perioperative change
Algra [48]	2014	Netherlands	RCT	37	15D (±21)	Aortic arch	Temp	18°C	Pre, intra, postop	Background, continuity, seizure/ NR
Andropoulos [42]	2010	USA	Prosp	68	8D (IQR:5-14)	CHD	NR	NR	Pre, postop	Background, seizure/ Seizure treatment
Bachet [27]	1991	France	Retro	54	55Y (R:25-76)	Aortic arch	EEG	27°C	Intra	Continuity, ECI/ HCA strategy
Bavaria [21]	2001	USA	Retro	104	58Y (±15)	Acute type A	Both	>5 mins ECI & <3°C	Intra	ECI/ Cannulation site
Cefarelli [14]	2017	Netherlands	Retro	791	63Y (±11.8)	Aortic arch	Both	<18°C	Intra	Asymmetry, ECI/ NR
Chen [32]	2009	USA	Prosp	122	6D (Ra:1-177)	CHD	Temp	18°C	Postop	Seizure/ Seizure treatment
Cheung [16]	1998	USA	Prosp	18	68Y (IQR:49-77)	Aortic arch	EEG	ECI	Intra	Continuity, ECI/ HCA strategy
Drury [33]	2013	New Zealand	Prosp	18	39M (Ra:37-41)	TGA	Temp	22°C	Intra, postop	Amplitude, seizure/ NR
Feyissa [40]	2016	USA	Retro	32	60Y (±11.7)	Asc aorta & arch	EEG	ECI	Pre, intra	Background, ECI, seizure/ NR
Ganzel [17]	1997	USA	Retro	30	61Y (±13.3)	Mix	EEG	ECI	Intra	Continuity, ECI/ HCA strategy
Gaynor [38]	2005	USA	Prosp	183	7D (Ra:1-188)	CHD	Temp	18 °C (IQR:15-21)	Pre, postop	Seizure/ Seizure treatment
Gaynor* [49]	2013			132	4Y					
Ghincea [31]	2021	USA	Retro	364	61Y (IQR:51-68)	Aortic arch	Temp	B:27°C (IQR: 25-28)	Intra	Asymmetry, background, frequency/ HCA strategy, postop care/imaging
Hayashida [20]	2007	Japan	Prosp	20	67Y (±9.6)	Aortic arch	Temp	N: 18°C; R: 20°C	Intra	Continuity/ NR
Hirotani [25]	2000	Japan	Prosp	75	Ra:21-83Y	Mix	EEG	2-3°C<ECI	Intra	ECI/ NR
Huang [37]	2007	China	RCT	24	8M (IQR:5-13)	VSD	Temp	28-30°C OR 18°C	Pre, postop	Background/ NR
Iwamoto [46]	1990	Japan	Prosp	75	6Y (±3)	CHD	NR	NR	Pre, postop	Background/ NR
Jacobs [22]	2001	Netherlands	Prosp	50	47Y (Ra:22-70)	Asc aorta & arch	Temp	28–30°C	Intra	Asymmetry, continuity/ ACP strategy
James [19]	2014	USA	Retro	325	58Y (±14)	Prox/asc aorta, arch	EEG	ECI	Intra	Asymmetry, ECI/ NR
Keenan [15]	2016	USA	Retro	71	64Y (IQR:53-69)	Aortic arch	Both	28°C	Intra	Continuity/ ACP/HCA strategy
Ma [13]	2020	USA	Retro	16	NR	Prox aorta & arch	EEG	ECI	Intra	Continuity, ECI/ NR

Mavroudis [34]	2018	USA	Prosp	10	4D (±1.5)	Aortic arch	Temp	18°C	Intra, postop	Amplitude, continuity, seizure/ NR
Mierbekov [26]	1997	Russia	Prosp	9	Ra:13-66Y	Thoracic aorta	NR	13.5°C (±0.5)	Intra	Continuity/HCA strategy
Mizrahi [39]	1989	USA	Prosp	56	58Y (±12)	Asc aorta & arch	EEG	2°C < ECI	Pre, intra	Amplitude, continuity, ECI/ HCA strategy
Murashita [18]	2016	USA	Retro	141	59Y (±14.6)	Aortic arch	Both	ECI	Intra	Asymmetry, continuity, ECI, seizure/ HCA strategy
Naim [6]	2015	USA	Retro	161	5D (IQR:3-7)	CHD	Temp	NR	Postop	Seizure/ Seizure treatment
Newburger [47] Bellinger[¥] [45] Helmers[¥] [50] Helmers[¥] [44]	1993 1995 1996 1997	USA	RCT	171	10D (±11.3)	TGA	Temp	<18°C	Pre, intra, postop	Background, continuity, seizure/ Seizure treatment
Raja [51]	2003	USA	Retro	27	Ra:9-90D	HLHS	NR	NR	Pre, postop	Background, seizure/ NR
Rung [28]	1991	USA	Retro	15	6M (±1.2)	CHD	Temp	N:15-17°C R:20-22°C	Intra	Amplitude, frequency, seizure/ HCA strategy
Seleznev [30]	2002	Russia	Retro	42	45Y (Ra:14-66)	Asc aorta & arch	Temp	14-15°C	Intra	ECI/ NR
Seltzer [35] Seltzer* [41]	2014 2016	USA	Prosp	32 21	10D (±9.4) 7D (±2.4)	CHD	Temp	21.2°C (±2.2)	Pre, intra, postop	Background, continuity, ECI, seizure/ NR
Stecker [23] Stecker* [24]	2001	USA	Prosp	109	65Y (±13.4)	Thoracic aorta	EEG	ECI	Intra	Continuity, ECI/ HCA strategy
Tobochnik [36]	2014	USA	Retro	6	64Y (IQR:42-68)	Aortic arch	Temp	20°C	Pre, intra	Background, asymmetry, continuity, seizure/ NR
Toet [43]	2005	Netherlands	Prosp	20	8D (IQR:6-10)	TGA	Temp	<21°C	Pre, intra, postop	Background, continuity, seizure/ seizure treatment
Westover [29]	2015	USA	Retro	11	62Y (Ra:36-79)	Thoracic aorta	Both	18°C & ECI	Intra	Amplitude, continuity, ECI frequency/ NR

[¥] indicates a sub-study of The Boston Circulatory Arrest Study; *Indicates a sub-study; Prosp: Prospective cohort; Retro: Retrospective cohort; RCT: Randomised controlled trial; D: Days; IQR: Interquartile range; Ra: Range; Y: Years; M: Months; NR: Not reported; CHD: Congenital heart disease; TGA: Transposition of the great arteries; HLHS: Hypoplastic left heart syndrome; Asc: Ascending; Mix: Mixture of heart diseases which require surgical intervention; VSD: Ventricular septal defect; Prox: Proximal; HCA: Hypothermic circulatory arrest; EEG: Electroencephalography; Both: Temperature and EEG used as guide; Temp: Temperature; ECI: Electrocerebral inactivity; N: Nasopharyngeal; R: Rectal; B: Bladder; Pre: Preoperative; Postop: Postoperative; Intra: Intraoperative; ACP: Antegrade cerebral perfusion

REFERENCES

[1] Hagl C, Khaladj N, Karck M, Kallenbach K, Leyh R, Winterhalter M *et al*. Hypothermic circulatory arrest during ascending and aortic arch surgery: the theoretical impact of different cerebral perfusion techniques and other methods of cerebral protection. *Eur J Cardiothorac Surg* 2003;24:371–378.

[2] Mebius MJ, Kooi EMW, Bilardo CM, Bos AF. Brain Injury and Neurodevelopmental Outcome in Congenital Heart Disease: A Systematic Review. *Pediatrics* 2017;140:e20164055.

[3] Patel N, Minhas JS, Chung EML. Risk Factors Associated with Cognitive Decline after Cardiac Surgery: A Systematic Review. *Cardiovasc Psychiatry Neurol* 2015;2015:370612.

[4] Creutzfeldt O, Houchin J. Neuronal basis of EEG waves In Remond A (ed) Handbook of Electroencephalography and Clinical Neurophysiology, Vol. 2, Amsterdam: Elsevier 1974:51-54

[5] Arrowsmith JE, Ganugapenta MSSR. Intraoperative Brain Monitoring in Cardiac Surgery in Bonser RS, Pagano D, Haverich A (eds) Brain Protection in Cardiac Surgery. London: Springer 2010:83–111.

[6] Naim MY, Gaynor JW, Chen J, Nicolson SC, Fuller S, Spray TL *et al*. Subclinical seizures identified by postoperative electroencephalographic monitoring are common after neonatal cardiac surgery. *J Thorac Cardiovasc Surg* 2015;150:169–180.

[7] De Paulis R, Czerny M, Weltert L, Bavaria J, Borger MA, Carrel TP *et al*. Current trends in cannulation and neuroprotection during surgery of the aortic arch in Europe. *Eur J Cardiothorac Surg* 2015;47:917–923.

[8] Isley MR, Edmonds HL, Stecker M. Guidelines for intraoperative neuromonitoring using raw (analog or digital waveforms) and quantitative electroencephalography: a position statement by the American Society of Neurophysiological Monitoring. *J Clin Monit Comput* 2009;23:369–390.

[9] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ *et al*. Cochrane Handbook for Systematic Reviews of Interventions. 2nd Edition. Chichester (UK): John Wiley & Sons 2019.

[10] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffman TC, Mulrow CD *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;n71.

[11] Wells G, Shea B, O'Connell J, Robertson J, Peterson V, Welch V et al. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analysis. Available at http://www.ohri.ca/ programs/clinical_epidemiology/oxfordasp. Accessed April 13, 2021.

[12] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;l4898.

[13] Ma O, Crepeau AZ, Dutta A, Bliss DW. Anticipating Postoperative Delirium During Burst Suppression Using Electroencephalography. *IEEE Trans Biomed Eng* 2020;67:2659–2668.

[14] Cefarelli M, Murana G, Surace GG, Castrovinci S, Jafrancesco G, Kelder JC *et al*. Elective Aortic Arch Repair: Factors Influencing Neurologic Outcome in 791 Patients. *Ann Thorac Surg* 2017;104: 2016–2023.

[15] Keenan JE, Wang H, Ganapathi AM, Englum BR, Kale E, Mathew JP *et al*. Electroencephalography During Hemiarch Replacement With Moderate Hypothermic Circulatory Arrest. *Ann Thorac Surg* 2016;101:631–637.

[16] Cheung AT, Bavaria JE, Weiss SJ, Patterson T, Stecker MM. Neurophysiologic effects of retrograde cerebral perfusion used for aortic reconstruction. *J Cardiothorac Vasc Anesth* 1998;12:252–259.

[17] Ganzel BL, Edmonds HL, Pank JR, Goldsmith LJ. Neurophysiologic monitoring to assure delivery of retrograde cerebral perfusion. *J Thorac Cardiovasc Surg* 1997;113:10.

[18] Murashita T, Pochettino A. Intraoperative Electroencephalogram-Guided Deep Hypothermia Plus Antegrade and/or Retrograde Cerebral Perfusion During Aortic Arch Surgery. *J Card Surg* 2016;31:216–219.

[19] James ML, Andersen ND, Swaminathan M, Phillips-Bute B, Hanna JM, Smigla GR *et al*. Predictors of electrocerebral inactivity with deep hypothermia. *J Thorac Cardiovasc Surg* 2014;147:1002–1007.

[20] Hayashida M, Sekiyama H, Orii R, Chinzei M, Ogawa M, Arita H *et al*. Effects of Deep Hypothermic Circulatory Arrest With Retrograde Cerebral Perfusion on Electroencephalographic Bispectral Index and Suppression Ratio. *J Cardiothorac Vasc Anesth* 2007;21:61–67.

[21] Bavaria JE, Pochettino A, Brinster DR, Gorman RC, McGavery ML, Gorman JH *et al*. New Paradigms and Improved Results for the Surgical Treatment of Acute Type A Dissection. *Ann Surg* 2001;234:336–343.

[22] Jacobs MJ, de Mol BA, Veldman DJ. Aortic arch and proximal supraaortic arterial repair under continuous antegrade cerebral perfusion and moderate hypothermia. *Cardiovasc Surg* 2001;9:396–402.

[23] Stecker MM, Cheung AT, Pochettino A, Kent GP, Patterson T, Weiss SJ *et al*. Deep hypothermic circulatory arrest: I. Effects of cooling on electroencephalogram and evoked potentials. *Ann Thorac Surg* 2001;71:14–21.

[24] Stecker MM, Cheung AT, Pochettino A, Kent GP, Patterson T, Weiss SJ *et al*. Deep hypothermic circulatory arrest: II. Changes in electroencephalogram and evoked potentials during rewarming. *Ann Thorac Surg* 2001;71:22–28.

[25] Hirotani T, Kameda T, Kumamoto T, Shirota S. Aortic arch repair using hypothermic circulatory arrest technique associated with pharmacological brain protection. *Eur J Cardiothorac Surg* 2000;18:545–549.

[26] Miyerbekov EM, Flerov EV, Dement'eva II, Seleznev MN, Kukaeva EA, Sablin IN. Changes in bioelectric activity and metabolism of the brain during surgery of the aorta under deep hypothermic arrest of circulation. *Anesteziol Reanimatol* 1997;45–49.

[27] Bachet J, Guilmet D, Goudot B, Termignon JL, Teodori G, Dreyfus G *et al*. Cold cerebroplegia. A new technique of cerebral protection during operations on the transverse aortic arch. *J Thorac Cardiovasc Surg* 1991;102:85–94.

[28] Rung GW, Scott Wickey G, Myers JL, Salus JE, Hensley FA, Martin DE. Thiopental as an adjunct to hypothermia for EEG suppression in infants prior to circulatory arrest. *J Cardiothorac Vasc Anesth* 1991;5:337–342.

[29] Westover MB, Ching S, Kumaraswamy VM, Akeju SO, Pierce E, Cash SS *et al*. The human burst suppression electroencephalogram of deep hypothermia. *Clin Neurophysiol* 2015;126:1901–1914.

[30] Seleznev MN, Babalian GV, Evdokimov ME, Guleshov VA, Dement'eva II, Shishlo LA et al. Anesthesia in surgical treatment of the ascending aorta-arch aneurysms. Anesteziol. Reanimatol 2002;4-7.

[31] Ghincea CV, Anderson DA, Ikeno Y, Roda GF, Eldeiry M, Bronsert M et al. Utility of neuromonitoring in hypothermic circulatory arrest cases for early detection of stroke: Listening through the noise. J Thorac Cardiovasc Surg 2021;162(4):1035-1045.

[32] Chen J, Zimmerman RA, Jarvik GP, Nord AS, Clancy RR, Wernovsky G *et al*. Perioperative Stroke in Infants Undergoing Open Heart Operations for Congenital Heart Disease. *Ann Thorac Surg* 2009;88:823–829.

[33] Drury PP, Gunn AJ, Bennet L, Ganeshalingham A, Finucane K, Buckley D *et al*. Deep hypothermic circulatory arrest during the arterial switch operation is associated with reduction in cerebral oxygen extraction but no increase in white matter injury. *J Thorac Cardiovasc Surg* 2013;146:1327–1333.

[34] Mavroudis CD, Mensah-Brown KG, Ko TS, Boorady TW, Massey SL, Abend NS *et al*. Electroencephalographic Response to Deep Hypothermic Circulatory Arrest in Neonatal Swine and Humans. *Ann Thorac Surg* 2018;106:1841–1846.

[35] Seltzer LE, Swartz M, Kwon JM, Burchfiel J, Alfieris GM, Guillet R. Intraoperative Electroencephalography Predicts Postoperative Seizures in Infants With Congenital Heart Disease. *Pediatr Neurol* 2014;50:313–317.

[36] Tobochnik SD, Guy TS, Pai SS, Jacobson MP, Gutierrez CA. EEG Asymmetry During Aortic Arch Surgeries Associated With Selective Preferential Cerebral Hypothermia. *J Clin Neurophysiol* 2014;31:232–235.

[37] Huang J-H, Su Z-K, Wang S-M. Near-Infrared Spectroscopy Monitoring of Brain Oxygen in Infant Cardiac Surgery. *Asian Cardiovasc Thorac Ann* 2007;15:194–199.

[38] Gaynor JW, Nicolson SC, Jarvik GP, Wernovsky G, Montenegro LM, Burnham NB *et al*. Increasing duration of deep hypothermic circulatory arrest is associated with an increased incidence of postoperative electroencephalographic seizures. *J Thorac Cardiovasc Surg* 2005;130:1278–1286.

[39] Mizrahi EM, Patel VM, Crawford ES, Coselli JS, Hess KR. Hypothermic-induced electrocerebral silence, prolonged circulatory arrest, and cerebral protection during cardiovascular surgery. *Electroencephalogr Clin Neurophysiol* 1989;72:81–85.

[40] Feyissa AM, Pochettino A, Bower TC, Nuttall GA, Britton JW. Rhythmic electrographic discharges during deep hypothermic circulatory arrest. *Clin Neurophysiol* 2016;127:1901–1906.

[41] Seltzer L, Swartz MF, Kwon J, Burchfiel J, Cholette JM, Wang H *et al*. Neurodevelopmental outcomes after neonatal cardiac surgery: Role of cortical isoelectric activity. *J Thorac Cardiovasc Surg* 2016;151:1137–1144.

[42] Andropoulos DB, Mizrahi EM, Hrachovy RA, Stayer SA, Stark AR, Heinle JS *et al.* Electroencephalographic Seizures After Neonatal Cardiac Surgery with High-Flow Cardiopulmonary Bypass. *Anesth Analg* 2010;110:1680–1685.

[43] Toet MC, Flinterman A, van de Laar I, de Vries J, Bennink GBWE, Uiterwaal CSPM *et al*. Cerebral oxygen saturation and electrical brain activity before, during, and up to 36 hours after arterial switch procedure in neonates without pre-existing brain damage: its relationship to neurodevelopmental outcome. *Exp Brain Res* 2005;165:343–350.

[44] Helmers SL, Wypij D, Constantinou JE, Newburger JW, Hickey PR, Carrazana EJ *et al*. Perioperative electroencephalographic seizures in infants undergoing repair of complex congenital cardiac defects. *Electroencephalogr Clin Neurophysiol* 1997;102:27–36.

[45] Bellinger DC, Jonas RA, Rappaport LA, Wypij D, Wernovsky G, Kuban KC *et al*. Developmental and Neurologic Status of Children after Heart Surgery with Hypothermic Circulatory Arrest or Low-Flow Cardiopulmonary Bypass. *N Engl J Med* 1995;332:549–555.

[46] Iwamoto I, Baba H, Koga Y, Uchida N, Matsuo K, Ishii K, *et al*. The relation between EEG and mental development following cardiac surgery performed under simple deep hypothermia in children. *Jpn J Surg* 1990;20:158–162.

[47] Newburger JW, Jonas RA, Wernovsky G, Wypij D, Hickey PR, Kuban K, *et al.* A comparison of the perioperative neurologic effects of hypothermic circulatory arrest versus low-flow cardiopulmonary bypass in infant heart surgery. *N Engl J Med* 1993;329:1057-64.

[48] Algra SO, Jansen NJG, van der Tweel I, Schouten NJ, Groenendaal F, Toet M *et al*. Neurological Injury After Neonatal Cardiac Surgery: A Randomized, Controlled Trial of 2 Perfusion Techniques. *Circulation* 2014;129:224–233.

[49] Gaynor JW, Jarvik GP, Gerdes M, Kim DS, Rajagopalan R, Bernbaum J *et al*. Postoperative electroencephalographic seizures are associated with deficits in executive function and social behaviors at 4 years of age following cardiac surgery in infancy. *J Thorac Cardiovasc Surg* 2013;146:132–139.

[50] Helmers SL, Kull L, Constantinou JE, Holmes GL. Electroencephalographic Monitoring of Infants during Repair of Complex Cardiac Defects. *Am J Electroneurodiagnostic Technol* 1996;36:133–147.

[51] Raja R, Johnston JK, Fitts JA, Bailey LL, Chinnock RE, Ashwal S. Post-transplant seizures in infants with hypoplastic left heart syndrome. *Pediatr Neurol* 2003;28:370–378.

[52] Thomas M, Li Z, Cook DJ, Greason KL, Sundt TM. Contemporary results of open aortic arch surgery. *J Thorac Cardiovasc Surg* 2012;144:838–844.

[53] Nuwer MR, Comi G, Emerson R, Fuglsang-Frederiksen A, Guérit JM, Hinrichs H *et al*. IFCN standards for digital recording of clinical EEG. International Federation of Clinical Neurophysiology. *Electroencephalogr Clin Neurophysiol* 1998;106:259–261.

[54] Shellhaas RA, Chang T, Tsuchida T, Scher MS, Riviello JJ, Abend NS *et al*. The American Clinical Neurophysiology Society's Guideline on Continuous Electroencephalography Monitoring in Neonates. *J Clin Neurophysiol* 2011;28:611-617.

[55] Tsuchida TN, Wusthoff CJ, Shellhaas RA, Abend NS, Hahn CD, Sullivan JE *et al*. American Clinical Neurophysiology Society Standardized EEG Terminology and Categorization for the Description of Continuous EEG Monitoring in Neonates: Report of the American Clinical Neurophysiology Society Critical Care Monitoring Committee. *J Clin Neurophysiol* 2013;30:161-173.

[56] Kuratani J, Pearl PL, Sullivan LR, Riel-Romero RMS, Cheek J, Stecker MM *et al*. American Clinical Neurophysiology Society Guideline 5: Minimum Technical Standards for Pediatric Electroencephalography. *Neurodiagnostic J* 2016;56:266–275.

[57] Sinha SR, Sullivan LR, Sabau D, San-Juan D, Dombrowski KE, Halford JJ *et al*. American Clinical Neurophysiology Society Guideline 1: Minimum Technical Requirements for Performing Clinical Electroencephalography. *Neurodiagnostic J* 2016;56:235–244.

[58] Seeck M, Koessler L, Bast T, Leijten F, Michel C, Baumgartner C *et al*. The standardized EEG electrode array of the IFCN. *Clin Neurophysiol* 2017;128:2070–2077.

[59] Hirsch LJ, Fong MWK, Leitinger M, LaRoche S, Beniczky S, Abend NS et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2021 Version. *J Clin Neurophysiol* 2021;38:1–29.

[60] Kirkham FJ, Wade AM, McElduff F, Boyd SG, Tasker RC, Edwards M *et al*. Seizures in 204 comatose children: incidence and outcome. *Intensive Care Med* 2012;38:853–862.

[61] Laccheo I, Sonmezturk H, Bhatt AB, Tomycz L, Shi Y, Ringel M *et al*. Non-convulsive Status Epilepticus and Non-convulsive Seizures in Neurological ICU Patients. *Neurocrit Care* 2015;22:202–211.

[62] Mokrushin AA, Pavlinova LI, Borovikov SE. Influence of cooling rate on activity of ionotropic glutamate receptors in brain slices at hypothermia. *J Therm Biol* 2014;44:5–13.

[63] Gordan ML, Kellermann K, Blobner M, Nollert G, Kochs EF, Jungwirth B. Fast rewarming after deep hypothermic circulatory arrest in rats impairs histologic outcome and increases NFκB expression in the brain. *Perfusion* 2010;25:349–354.

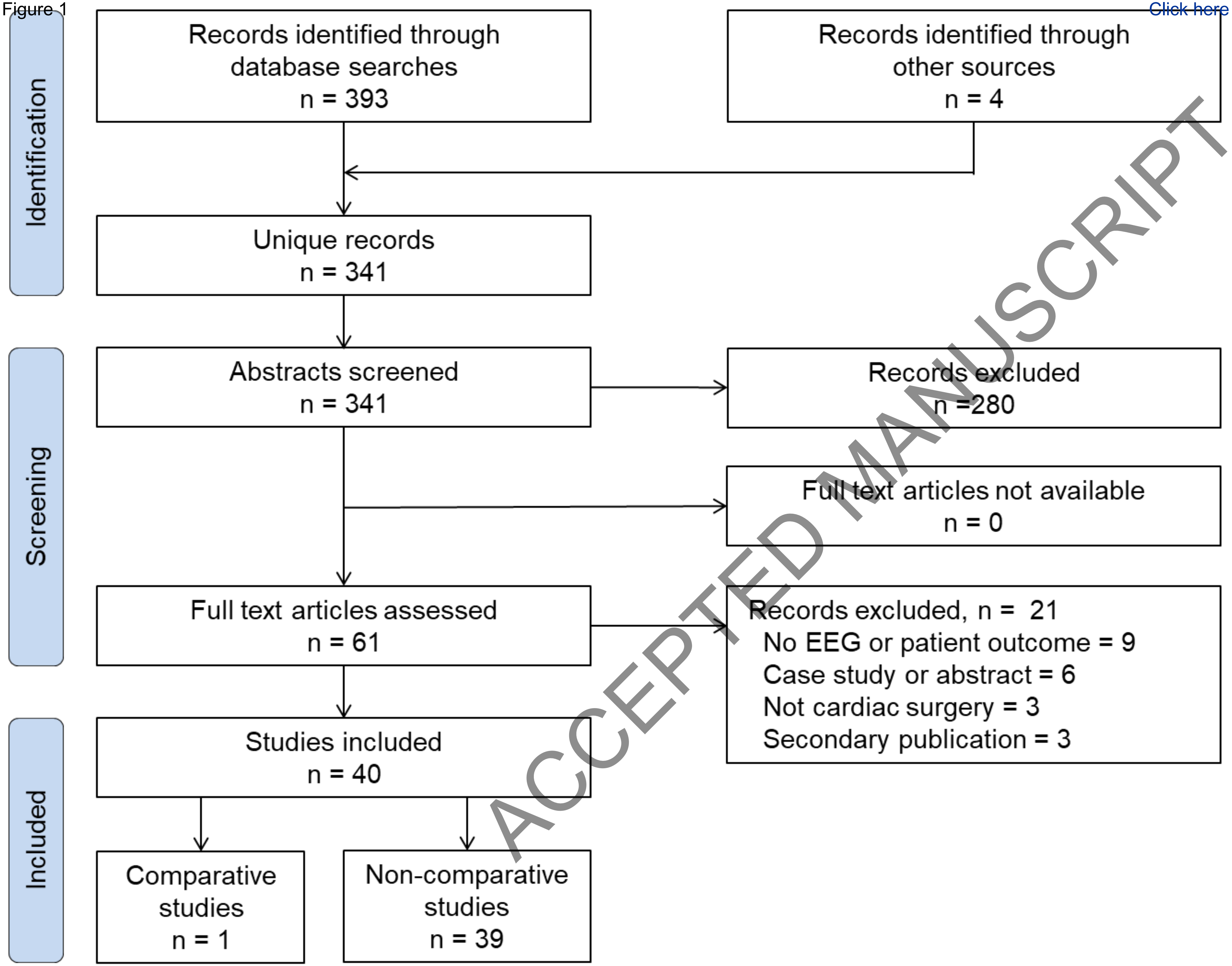
[64] Grigore AM, Grocott HP, Mathew JP, Phillips-Bute B, Stanley TO, Butler A *et al*. The Rewarming Rate and Increased Peak Temperature Alter Neurocognitive Outcome After Cardiac Surgery. Anesth Analg 2002;94:4-10.

[65] Czerny M, Schmidli J, Adler S, van den Berg JC, Bertoglio L, Carrel T *et al*. Current options and recommendations for the treatment of thoracic aortic pathologies involving the aortic arch: an expert consensus document of the European Association for Cardio-Thoracic surgery (EACTS) and the European Society for Vascular Surgery (ESVS). *Eur J Cardiothorac Surg* 2019;55:133–162.

[66] Alkhatip AAAMM, Kamel MG, Farag EM, Elayashy M, Farag A, Yassin HM *et al*. Deep Hypothermic Circulatory Arrest in the Pediatric Population Undergoing Cardiac Surgery With Electroencephalography Monitoring: A Systematic Review and Meta-Analysis. *J Cardiothorac Vasc Anesth* 2021;35:2875–2888.

[67] Drury NE, Yim I, Patel AJ, Oswald NK, Chong C-R, Stickley J *et al*. Cardioplegia in paediatric cardiac surgery: a systematic review of randomized controlled trials. *Interact Cardiovasc Thorac Surg* 2019;28:144–150.

Figure 1



Identification
Records identified through database searches n = 393
Records identified through other sources n = 4
Unique records n = 341
Screening
Abstracts screened n = 341
Records excluded n = 280
Full text articles not available n = 0
Full text articles assessed n = 61
Records excluded, n = 21
No EEG or patient outcome = 9
Case study or abstract = 6
Not cardiac surgery = 3
Secondary publication = 3
Included
Studies included n = 40
Comparative studies n = 1
Non-comparative studies n = 39

Central image

EEG burst-suppression before electrocerebral inactivity in hypothermic circulatory arrest