Incidence of postoperative seizures in neonates following cardiac surgery with regional cerebral perfusion and deep hypothermic circulatory arrest

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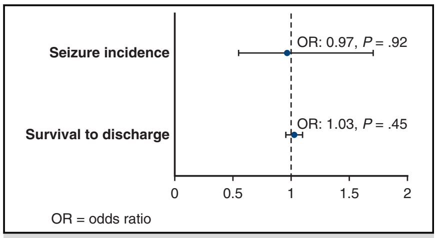
ABSTRACT

Objectives: Historically, our center has primarily used deep hypothermic circulatory arrest, but in recent years some surgeons have selectively used regional cerebral perfusion as an alternative. We aimed to compare the incidence of postoperative electroencephalographic seizure incidence in neonates undergoing surgery with regional cerebral perfusion and deep hypothermic circulatory arrest.

Methods: A retrospective analysis was performed in neonates who underwent surgery between 2012 and 2022 with either deep hypothermic circulatory arrest or regional cerebral perfusion with routine postoperative continuous electroencephalography monitoring for 48 hours. Propensity matching was performed to compare postoperative seizure risk between the 2 groups.

Results: Among 1136 neonates undergoing cardiac surgery with cardiopulmonary bypass, regional cerebral perfusion was performed in 99 (8.7%) and deep hypothermic circulatory arrest in 604 (53%). The median duration of regional cerebral perfusion was 49 minutes (interquartile range, 38-68) and deep hypothermic circulatory arrest was 41 minutes (interquartile range, 31-49). The regional cerebral perfusion group had significantly longer total support, cardiopulmonary bypass, and aortic cross-clamp times. Overall seizure incidence was 11% (N = 76) and 13% (N = 35) in the most recent era (2019-2022). The unadjusted seizure incidence was similar in neonates undergoing regional cerebral perfusion (N = 12, 12%) and deep hypothermic circulatory arrest (N = 64, 11%). After propensity matching, the seizure incidence was similar in neonates undergoing regional cerebral perfusion (N = 12, 12%) and deep hypothermic circulatory arrest (N = 37, 12%) (odds ratio, 0.97; 95% CI, 0.55-1.71; *P* = .92).

Conclusions: In this contemporary single-center experience, the incorporation of regional cerebral perfusion did not result in a change in seizure incidence in comparison with deep hypothermic circulatory arrest. However, unmeasured confounders may have impacted these findings. Further studies are needed to determine the impact, if any, of regional cerebral perfusion on postoperative seizure incidence. (JTCVS Open 2023;16:771-83)



RCP compared with DHCA.

CENTRAL MESSAGE

In neonates undergoing cardiac surgery, use of RCP was not associated with a reduction in postoperative seizures.

PERSPECTIVE

In this contemporary study comparing postoperative seizure incidence in a large cohort of neonates, the use of RCP was not associated with a lower seizure rate compared with DHCA. Given the variability in RCP flow rates and intraoperative neuromonitoring within and across institutions, further studies are needed to delineate the utility of RCP as a neuroprotective strategy.

See Discussion on page 784.

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Abbreviations and Acronyms

- cEEG = continuous electroencephalography
- CPB = cardiopulmonary bypass
- DHCA = deep hypothermic circulatory arrest
- EEG = electroencephalography
- IQR = interquartile range
- OR = odds ratio
- RCP = regional cerebral perfusion
- SMD = standardized mean difference
- STAT = Society of Thoracic Surgeons-European Association for Cardiothoracic Surgery

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As survival of neonates with congenital heart disease has improved, focus has shifted from preventing mortality to improving long-term outcomes and quality of life. Long-term neurodevelopmental impairment remains a significant source of morbidity in survivors of neonatal cardiac surgery.[1] For operations facilitated by a bloodless field, the use of deep hypothermic circulatory arrest (DHCA) as a neuroprotective strategy may contribute to neurologic injury by exposure to cerebral ischemia. Regional cerebral perfusion (RCP) was developed as an alternative to DHCA[2] that could achieve a similar surgical field while providing some degree of cerebral perfusion with the goal of preventing hypoxic ischemic brain injury and hopefully ensuring cerebral protection. However, data comparing neurologic outcomes in patients undergoing DHCA and RCP are conflicting.[3-6] In addition, there is evidence that the use of DHCA in neonates may not impact neurodevelopment.[7] Consequently, there is practice variation among pediatric cardiac surgeons between use of DHCA and RCP.[8]

Although historically our center has primarily used DHCA, in recent years some surgeons have selectively used RCP as an alternative. Given postoperative seizures in neonates after cardiac surgery have been linked to adverse long-term neurodevelopmental outcomes[9] and the lack of consensus regarding the optimal strategy for neuroprotection, we aimed to compare the incidence of postoperative electroencephalography (EEG) seizures between neonates undergoing cardiac surgery with RCP and DHCA.

MATERIAL AND METHODS

Participants

We performed a retrospective analysis of neonates who underwent surgery with DHCA or RCP at less than corrected 44 weeks gestational age from June 2012 to December 2022. Routine postoperative continuous EEG (cEEG) monitoring was implemented at our institution in 2012, and all patients during the study period underwent routine cEEG monitoring. For patients with multiple surgeries in the neonatal period, only the index surgery was included. Exclusion criteria included (1) cases using isolated continuous cardiopulmonary bypass (CPB), (2) neonates who did not undergo 48 hours of postoperative cEEG monitoring, and (3) neonates who had an operation that was not classified by the Society of Thoracic Surgeons European Association for Cardiothoracic Surgery (STAT) category. The Institutional Review Board (IRB) committee at the Children's Hospital of Philadelphia approved the study protocol and publication of data (IRB 13-010704, June 15, 2012). Patient written consent for the publication of the study data was waived by the IRB given the retrospective nature of the study.

Surgical Technique

Surgeries were performed by 8 surgeons with a cardiac anesthesia team. DHCA or RCP was used at the discretion of the surgeon. Patients undergoing DHCA were cooled from normothermia to a temperature of 18 degrees over 15 to 20 minutes. A pH stat blood gas management strategy was used during cooling. Patients were rewarmed over approximately 22 minutes. An alpha stat blood gas management strategy was used during rewarming.

For patients undergoing RCP, flow rate was determined by the surgeon. Patients undergoing RCP were cooled to a temperature of 18 to 24 degrees at the discretion of the surgeon over 15 to 20 minutes. A pH stat blood gas management strategy was used during cooling. During RCP, an alpha stat blood gas management strategy was used. Patients were monitored on unifrontal or bifrontal near-infrared spectroscopy. Blood pressures were monitored on an upper-extremity arterial line. Patients were rewarmed over approximately 22 minutes. An alpha stat blood gas management strategy was used during rewarming.

Measures and Data Collection

The primary exposure variable was RCP. Patients were categorized into the RCP or DHCA group based on the predominant strategy used. The primary outcome was EEG seizure occurrence. Seizures were defined as an abnormal paroxysmal EEG event different from the background, lasting longer than 10 seconds (or less if associated with a clinical seizure), with a plausible EEG field that evolved in frequency, voltage, morphology, or spatial distribution. Information regarding preoperative, intraoperative, and postoperative patient clinical data was obtained from the electronic medical record. Data were collected and managed using a secure database, Research Electronic Data Capture.

Electroencephalography Monitoring

Continuous EEG monitoring was initiated within 6 hours of returning to the cardiac intensive care unit and continued for a minimum of 48 hours postoperatively, consistent with recent recommendations regarding use of cEEG monitoring in neonates at risk for seizures.[10,11] cEEG monitoring was performed with the international 10-20 system (modified for neonates) using portable acquisition machines networked to enable EEG review at the bedside, from multiple sites in the hospital, and remotely. In infants with EEG seizures, cEEG monitoring was continued for 24 hours after the termination of the last seizure.

Propensity Matching

We used propensity score–matched analysis to reduce selection bias and account for differences between the RCP and DHCA groups. Propensity scores were estimated using a logistic regression model in which the dependent variable was RCP, and the independent variables were gestational age and STAT class.

The MatchIt package in R was used to perform 3:1 nearest neighbor propensity score matching without replacement. The caliper width for matching was set at 0.2. Before matching, patients in the RCP group (N = 99) had a mean propensity score of 0.1477 and those in the DHCA group (N = 604) had a mean propensity score of 0.1397. After matching, the mean propensity scores were 0.1477 and 0.1476 for the RCP (N = 99) and DHCA (N = 297) groups, respectively. A Love plot (Figure E1) was created to assess the covariate balance before and after matching; standardized mean differences (SMDs) for the matched variables were below 0.10.

Statistical Analysis

Patient demographics, clinical characteristics, and outcomes were summarized using mean and SD or median and interquartile range (IQR) for continuous variables, as appropriate. Categorical data were summarized using counts and percentages. These statistics were calculated for overall study participants and grouped by the patient's support technique, RCP or DHCA. The results were evaluated for balance across groups before and after matching, with SMD values 0.20 or greater indicating imbalance.[12] Odds ratios (ORs) and their associated 95% CIs from a conditional logistic regression analysis were used to assess the strength of the association between EEG seizure incidence and support technique (RCP vs DHCA). All analyses were conducted using R software version 4.2.2 (R Core Team) and the MatchIt package.[13]

RESULTS

Among 1143 neonates who underwent surgery with CPB use during the study period, 703 met the inclusion criteria for this study (Figure 1). The support mechanism was RCP in 14% (N = 99) and DHCA in 86% (N = 604) of neonates. After propensity score matching, there were 99 patients in the RCP group and 297 patients in the DHCA group.

The median gestational age of the cohort was 39.0 weeks (IQR, 38.0-39.1). Sixteen percent (N = 65) of neonates had an identified genetic defect. Fifty-six percent (N = 220) of neonates had single ventricle defects. There were higher rates of prenatal diagnosis in the RCP group than in the DHCA group (96% vs 82%, SMD = 0.45). Patients in the RCP group had a smaller median birth head circumference compared with the DHCA group (33.0 cm vs 33.5 cm, SMD = 0.25). Table 1 lists patient demographics before and after propensity matching.

The median age at time of surgery in the cohort was 4.0 days (IQR, 3.0-6.0). Fifty-seven percent (N = 224) of neonates underwent a STAT category 5 operation, 40% (N = 160) of neonates underwent a STAT category 4 operation, and 3% (N = 12) of neonates underwent a STAT category 1-3 operation. Table 2 provides additional intraoperative characteristics of patients. Ninety-six percent (N = 95) of patients in the RCP group underwent surgery in the most recent surgical era (2019-2022). Patients in the

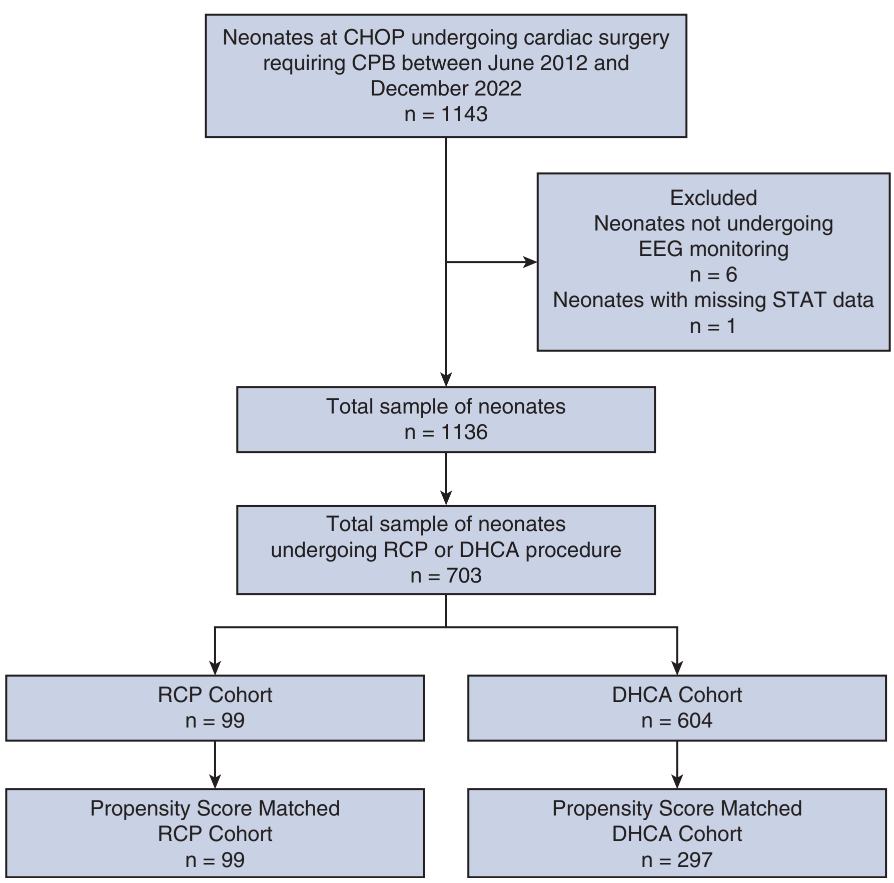


FIGURE 1. Patient selection.

TABLE 1. Demographic and preoperative characteristics of regional cerebral perfusion versus deep hypothermic circulatory arrest groups

	Before propensity score matching				After propensity score matching			
Variable	Overall N = 703*	RCP n = 99*	DHCA n = 604*	SMD†	Overall N = 396*	RCP n = 99*	DHCA n = 297*	SMD†
Gender				0.03				0.01
Female	278 (40%)	38 (38%)	240 (40%)		154 (39%)	38 (38%)	116 (39%)	
Male	425 (60%)	61 (62%)	364 (60%)		242 (61%)	61 (62%)	181 (61%)	
Race				**0.26**				**0.31**
White	385 (55%)	55 (56%)	330 (55%)		221 (56%)	55 (56%)	166 (56%)	
Black	107 (15%)	22 (22%)	85 (14%)		58 (15%)	22 (22%)	36 (12%)	
Other	211 (30%)	22 (22%)	189 (31%)		117 (30%)	22 (22%)	95 (32%)	
Prenatal diagnosis	580 (83%)	95 (96%)	485 (80%)	**0.50**	340 (86%)	95 (96%)	245 (82%)	**0.45**
Premature	130 (18%)	16 (16%)	114 (19%)	0.07	53 (13%)	16 (16%)	37 (12%)	0.11
Gestational age, wk	38.9 (37.9, 39.3)	39.0 (37.8, 39.1)	38.9 (37.9, 39.3)	0.02	39.0 (38.0, 39.1)	39.0 (37.8, 39.1)	39.0 (38.0, 39.1)	0.06
Birth weight, kg	3.1 (2.7, 3.5)	3.1 (2.8, 3.4)	3.1 (2.7, 3.5)	0.04	3.2 (2.8, 3.5)	3.1 (2.8, 3.4)	3.2 (2.8, 3.5)	0.15
Birth head circumference, cm	33.5 (32.0, 34.5)	33.0 (32.0, 34.0)	33.5 (32.4, 34.8)	**0.22**	33.5 (32.5, 34.5)	33.0 (32.0, 34.0)	33.5 (32.5, 34.5)	**0.25**
Maternal complications‡								
Maternal diabetes	65 (9%)	7 (7%)	58 (10%)	0.09	34 (9%)	7 (7%)	27 (9%)	0.07
Maternal pregnancy-induced hypertension	31 (4%)	4 (4%)	27 (4%)	0.02	17 (4%)	4 (4%)	13 (4%)	0.02
Pre-eclampsia	25 (4%)	2 (2%)	23 (4%)	0.11	14 (4%)	2 (2%)	12 (4%)	0.12
Eclampsia	1 (0%)	1 (1%)	0 (0%)	0.14	1 (0%)	1 (1%)	0 (0%)	0.14
HELLP	6 (1%)	0 (0%)	6 (1%)	0.14	2 (1%)	0 (0%)	2 (1%)	0.12
Genetic syndrome	141 (20%)	16 (16%)	125 (21%)	0.12	65 (16%)	16 (16%)	49 (16%)	0.01
Single ventricle	324 (46%)	58 (59%)	266 (44%)	**0.29**	220 (56%)	58 (59%)	162 (55%)	0.08
Cardiac abnormality				**0.62**				**0.42**
Single ventricle with arch obstruction	296 (42%)	58 (59%)	238 (39%)		210 (53%)	58 (59%)	152 (51%)	
Single ventricle without arch obstruction	28 (4%)	0 (0%)	28 (5%)		10 (3%)	0 (0%)	10 (3%)	
2 ventricles with arch obstruction	279 (40%)	38 (38%)	241 (40%)		141 (36%)	38 (38%)	103 (35%)	
2 ventricles without arch obstruction	100 (14%)	3 (3%)	97 (16%)		35 (9%)	3 (3%)	32 (11%)	
Preoperative seizures	8 (1%)	1 (1%)	7 (1%)	0.01	3 (1%)	1 (1%)	2 (1%)	0.04

RCP, Regional cerebral perfusion; *DHCA,* deep hypothermic circulatory arrest; *SMD,* standardized mean difference; *HELLP,* hemolysis, elevated liver enzymes and low platelets. *n (%). Median (IQR). †SMDs 0.20 or greater are bold to indicate imbalance between groups. ‡Patients may be in 2 or more categories.

RCP group were younger at the time of surgery (3.0 vs 5.0 days, SMD = 0.24). Patients in the RCP group had longer aortic crossclamp (74 vs 45 minutes), CPB (116 vs 45 minutes), and total support duration (170 vs 87 minutes), all SMD 0.20 or greater.

The median duration of RCP was 49 minutes (IQR, 38-68). Brief periods of DHCA were used in 54% (N = 53) of the RCP group with a median duration of 6 minutes (range, 1-21 minutes). The median RCP flow rate was 50 mL/kg/min with a minimum RCP flow rate of 25 mL/kg/min and a maximum RCP flow rate of 60 mL/kg/min. The median duration of DHCA was 39 minutes (IQR, 29-48) before matching and 41 minutes after matching (IQR, 31-49). Intermittent reperfusion was used in 1% (N = 7) of the DHCA group with a median duration of 5 minutes (range, 3-7 minutes).

EEG seizures occurred in 11% (N = 76) of the full cohort, and there was no difference in EEG seizure incidence between the RCP (12%, N = 12) and DHCA (11%, N = 64) subgroups (SMD = 0.05) (Figure 2). The EEG seizure incidence in the RCP (12%, N = 12) and DHCA (12%, N = 37) subgroups remained similar (OR, 0.97, 0.55-1.71 *P* = .92, Table 3) after propensity score matching. Patients with single ventricle physiology had a

TABLE 2. Intraoperative characteristics of regional cerebral perfusion versus deep hypothermic circulatory arrest groups

Variable	Before propensity score matching: Overall N = 703*	Before: RCP n = 99*	Before: DHCA n = 604*	Before: SMD†	After propensity score matching: Overall N = 396*	After: RCP n = 99*	After: DHCA n = 297*	After: SMD†
Year of surgery				**1.99**				1.76
2012-2015	228 (32%)	0 (0%)	228 (38%)		100 (25%)	0 (0%)	100 (34%)	
2016-2018	213 (30%)	4 (4%)	209 (35%)		103 (26%)	4 (4%)	99 (33%)	
2019-2022	262 (37%)	95 (96%)	167 (28%)		193 (49%)	95 (96%)	98 (33%)	
Age at surgery, d	5.0 (3.0, 7.0)	3.0 (3.0, 5.0)	5.0 (3.0, 7.0)	**0.33**	4.0 (3.0, 6.0)	3.0 (3.0, 5.0)	5.0 (3.0, 7.0)	**0.24**
Operation				**0.53**				**0.40**
BTT shunt on bypass	8 (1%)	0 (0%)	8 (1%)		1 (0%)	0 (0%)	1 (0%)	
Stage 1	295 (42%)	56 (57%)	239 (40%)		211 (53%)	56 (57%)	155 (52%)	
Complete 2 ventricle repair with arch reconstruction	202 (29%)	23 (23%)	179 (30%)		101 (26%)	23 (23%)	78 (26%)	
Complete 2 ventricle repair	79 (11%)	8 (8%)	71 (12%)		30 (8%)	8 (8%)	22 (7%)	
Arterial switch operation	7 (1%)	0 (0%)	7 (1%)		5 (1%)	0 (0%)	5 (2%)	
Arterial switch operation with arch reconstruction	23 (3%)	7 (7%)	16 (3%)		12 (3%)	7 (7%)	5 (2%)	
Other	89 (13%)	5 (5%)	84 (14%)		36 (9%)	5 (5%)	31 (10%)	
STAT Class				**0.29**				<0.001
Class 1 and 2	19 (3%)	1 (1%)	18 (3%)		4 (1%)	1 (1%)	3 (1%)	
Class 3	11 (2%)	2 (2%)	9 (1%)		8 (2%)	2 (2%)	6 (2%)	
Class 4	353 (50%)	40 (40%)	313 (52%)		160 (40%)	40 (40%)	120 (40%)	
Class 5	320 (46%)	56 (57%)	264 (44%)		224 (57%)	56 (57%)	168 (57%)	
Lowest temperature, centigrade	18.0 (17.5, 18.8)	18.0 (17.5, 20.0)	18.0 (17.5, 18.7)	**0.23**	18.0 (17.5, 19.0)	18.0 (17.5, 20.0)	18.0 (17.5, 18.7)	0.14
Aortic crossclamp duration, min	46.0 (36.0, 59.5)	74.0 (56.5, 104.5)	43.0 (34.0, 54.2)	**0.95**	50.0 (39.0, 65.0)	74.0 (56.5, 104.5)	45.0 (36.0, 55.0)	**0.94**
CPB duration, min	47.0 (40.0, 80.0)	116.0 (85.0, 164.5)	45.0 (39.0, 60.0)	**1.40**	50.0 (41.0, 92.8)	116.0 (85.0, 164.5)	45.0 (40.0, 58.0)	**1.44**
Total support time, min	90.0 (78.0, 121.0)	170.0 (130.5, 238.5)	87.0 (76.0, 106.0)	**1.43**	95.0 (82.0, 140.0)	170.0 (130.5, 238.5)	87.0 (78.0, 105.0)	**1.44**
Lowest intraoperative HCT	28.0 (26.0, 30.0)	28.0 (26.0, 29.0)	28.0 (26.0, 30.9)	**0.36**	28.9 (26.9, 30.2)	28.0 (26.0, 29.0)	29.0 (27.0, 31.0)	**0.41**

RCP, Regional cerebral perfusion; *DHCA,* deep hypothermic circulatory arrest; *SMD,* standardized mean difference; *BTT,* Blalock–Thomas–Taussig; *STAT,* Society of Thoracic Surgeons-European Association for Cardiothoracic Surgery; *CPB,* cardiopulmonary bypass; *HCT,* hematocrit. *n (%). Median (IQR). †SMDs 0.20 or greater are bold to indicate imbalance between groups.

higher incidence of seizures compared with those with biventricular physiology (18% [N = 39] for single ventricle patients, 6% [N = 10] for biventricular patients, SMD = 0.38) (Figure 3). The seizure incidence in the most recent surgical era 2019-2022 was 13.4%, which was increased compared with prior surgical eras, although

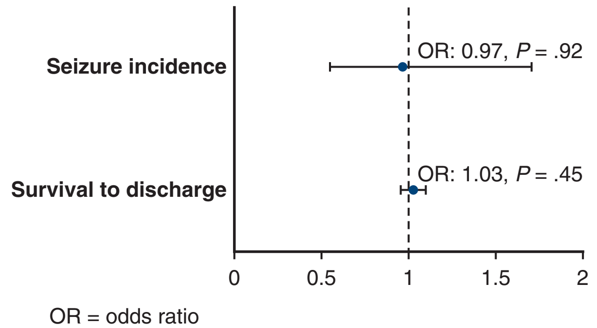


FIGURE 2. RCP compared with DHCA.

TABLE 3. Postoperative electroencephalographic seizure incidence in patients undergoing regional cerebral perfusion compared with deep hypothermic circulatory arrest

Outcomes	Characteristic	Univariable model: OR	95% CI	*P* value
Conditional logistic regression				
Seizures	RCP	0.97	0.55-1.71	.92
Survival to discharge	RCP	1.03	0.96-1.10	.45

OR, Odds ratio; *RCP,* regional cerebral perfusion.

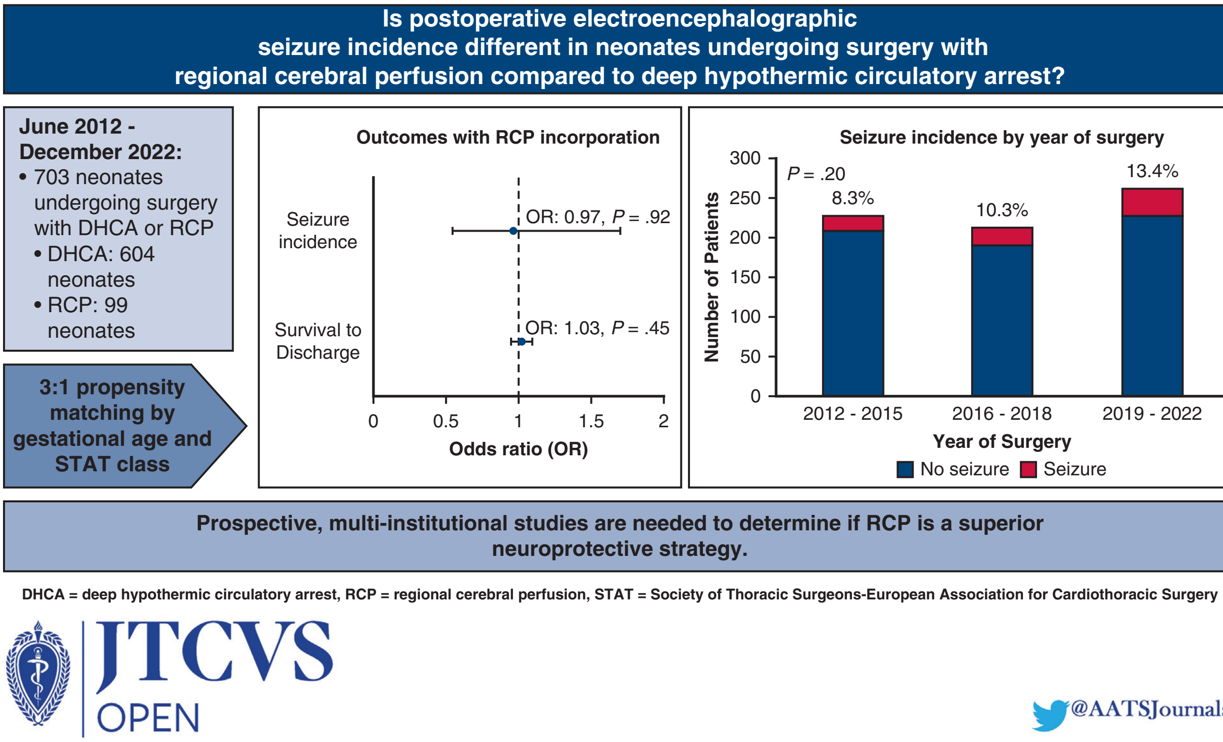


FIGURE 3. Graphical abstract. *OR,* Odds ratio.

this did not reach statistical significance ($P = .20$, Table 4). Figure 4 displays the relationship between EEG seizure incidence and RCP flow rate. The relationship between RCP and DHCA duration and seizure incidence is shown in Figures E2 and E3.

Table 5 displays postoperative outcomes. The incidence of cardiac arrest in the operating room was higher in the RCP group than in the DHCA group (5% vs 0.3%, SMD = 0.29) (Figure 3). Survival to discharge was not different between the 2 groups (91% [N = 90] for the RCP cohort vs 89% [N = 263] for the DHCA cohort, OR 1.03, 0.96, $P = .45$, Table 3).

DISCUSSION

In this contemporary study, we aimed to examine the impact of RCP compared with DHCA on postoperative EEG seizure incidence in a large cohort of neonates with both single and biventricular defects. We found no difference in postoperative EEG seizure incidence between patients who underwent surgery with RCP compared with DHCA both before and after propensity matching. Additionally, postoperative EEG seizure incidence in the most recent surgical era, 2019-2022, when most of the RCP cohort underwent surgery, was not lower compared with previous eras.

We used seizure occurrence as a surrogate for neurologic injury, because previous work from the Boston Circulatory Arrest Study demonstrated that in patients who underwent repair of d-transposition of the great arteries, the occurrence of postoperative seizures was most predictive of neurodevelopmental outcomes in adolescence.[9] Continuous EEG monitoring after surgeries with CPB is now recommended by the American Clinical Neurophysiology Society[10] and consistent with recent recommendations from the International League Against Epilepsy.[11] We implemented routine cEEG monitoring in neonates after surgery with CBP in 2012[14] before selective use of RCP.

The Boston Circulatory Arrest Study was one of the first studies to establish the link between postoperative seizures and neurologic injury, and also brought attention to the potential impact of DHCA on neurodevelopment. In comparison with infants who underwent repair with RCP, neonates with DHCA had a higher risk of clinical seizures in the postoperative period[15] and worse motor development at 8 years of age.[16] However, at 16 years of age, although the DHCA cohort had worse executive function and social cognition, there were no significant differences between the RCP and DHCA cohorts in other measures of neurodevelopment.[9]

TABLE 4. Seizure incidence by surgery year

Seizure	2012-2015 n = 228	2016-2018 n = 213	2019-2022 n = 262	*P* value*
Yes	19 (8.3%)	22 (10.3%)	35 (13.4%)	.20
No	209 (91.7%)	191 (89.7%)	227 (86.6%)	

**P* value obtained from chi-square test.

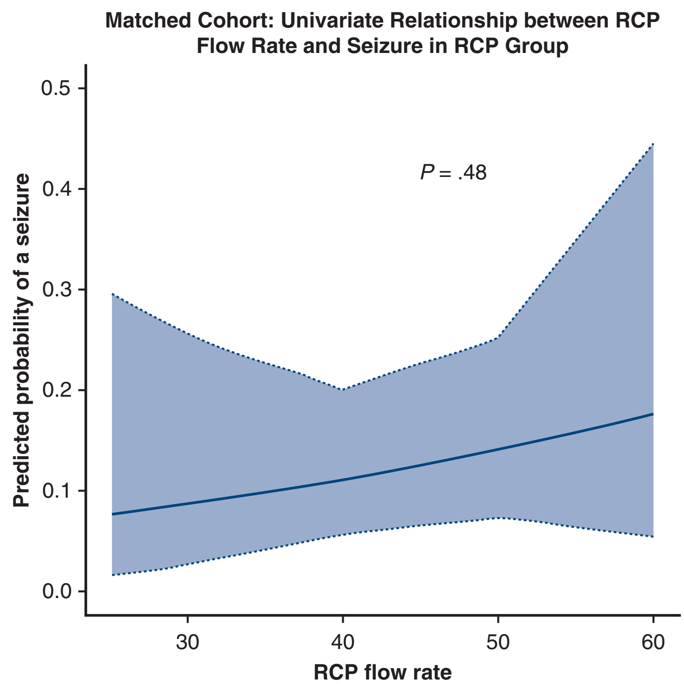


FIGURE 4. RCP flow rate and predicted probability of seizure occurrence. *RCP,* Regional cerebral perfusion.

Previous studies examining neurodevelopmental outcomes in patients undergoing RCP and DHCA have had mixed results, but there have been few studies comparing postoperative EEG seizure incidence between the 2 groups. A retrospective, single-center study of 1250 patients undergoing DHCA and RCP demonstrated a higher incidence of temporary and permanent neurologic dysfunction in patients undergoing DHCA.[17] Postoperative seizures were included as a type of neurologic dysfunction, but seizure incidence in each group was not reported. Another study randomized 37 neonates with both single ventricle and biventricular physiology to receive DHCA or RCP and did not find a difference in postoperative seizure incidence between the 2 groups, consistent with our findings.[18] The study reported an overall clinical and EEG seizure incidence of 19%, but it did not report the combined clinical and EEG only seizure incidence for each cohort. Additionally, there was no difference in new cerebral injury on postoperative brain magnetic resonance imaging or in motor and cognitive outcomes at 24 months of age between the groups.

Multiple other studies have demonstrated no difference in neurodevelopmental outcomes between patients undergoing DHCA and RCP. One study randomized 77 neonates with single ventricle anatomy to receive DHCA or RCP, and there was no difference in Bayley Scales of Infant Development scores between the 2 groups at 1 year of age.[5] Seizure incidence was not reported. Likewise, another study retrospectively assessed 29 infants with single ventricle defects who underwent DHCA or RCP, and there was no difference in development at 1 year of age.[6]

Of note, there is variation in RCP flow rates used in clinical practice and no consensus regarding the optimal flow rate, which may impact the negative findings of the previously summarized studies, as well as our current study. The RCP flow rate in our cohort ranged from 25 mL/kg/min to 60 mL/kg/min with a median flow rate of 50 mL/kg/min. Some institutions have reported neuromonitoring guided RCP flow titration with bifrontal near-infrared spectroscopy and transcranial dopplers to ensure the flow achieved with RCP matches the cerebral blood flow velocity at the patient's full flow hypothermic baseline before initiation of RCP.[19] With this strategy, RCP flow rates of up to 80 mL/kg/min have been reported, with elimination of new postoperative periventricular leukomalacia compared with historical control patients undergoing DHCA. The potential importance of optimizing RCP flow is also highlighted by multiple animal[20,21] and human models,[22] which suggest that RCP flow rates of 20 to 40 mL/kg/min may not provide adequate oxygen delivery to the cerebral circulation. The absence of a standard protocol to guide RCP flow titration and intraoperative neuromonitoring used during cases using RCP are limitations of our study and may contribute to our negative findings. Additionally, the parameters used to adjust RCP flow rate (near-infrared spectroscopy, mean arterial blood pressure) was also variable among surgeons, resulting in a wide range of RCP flow rates.

TABLE 5. Postoperative characteristics of regional cerebral perfusion versus deep hypothermic circulatory arrest groups

	Before propensity score matching				After propensity score matching			
Variable	Overall N = 703*	RCP n = 99*	DHCA n = 604*	SMD†	Overall N = 396*	RCP n = 99*	DHCA n = 297*	SMD†
ECMO onset in the operating room	22 (3%)	4 (4%)	18 (3%)	0.06	17 (4%)	4 (4%)	13 (4%)	0.02
ECMO onset in the CICU	45 (6%)	7 (7%)	38 (6%)	0.03	29 (7%)	7 (7%)	22 (7%)	0.01
Cardiac arrest onset in the operating room	7 (1%)	5 (5%)	2 (0%)	**0.30**	6 (2%)	5 (5%)	1 (0%)	**0.29**
Cardiac arrest onset in the CICU	52 (7%)	5 (5%)	47 (8%)	0.11	34 (9%)	5 (5%)	29 (10%)	0.18
Chest left open in operating room	249 (35%)	66 (67%)	183 (30%)	**0.78**	167 (42%)	66 (67%)	101 (34%)	**0.69**
Chest opened in the CICU	31 (4%)	3 (3%)	28 (5%)	0.08	21 (5%)	3 (3%)	18 (6%)	0.15
Inhaled nitric oxide from operating room	170 (24%)	22 (22%)	148 (25%)	0.05	93 (23%)	22 (22%)	71 (24%)	0.04
Postoperative infusions‡								
Fentanyl	448 (64%)	86 (87%)	362 (60%)	**0.64**	265 (67%)	86 (87%)	179 (60%)	**0.63**
Midazolam§	33 (5%)	4 (4%)	29 (5%)	0.04	19 (5%)	4 (4%)	15 (5%)	0.05
Ketamine	336 (48%)	32 (32%)	304 (50%)	**0.37**	180 (45%)	32 (32%)	148 (50%)	**0.36**
Morphine	61 (9%)	9 (9%)	52 (9%)	0.02	39 (10%)	9 (9%)	30 (10%)	0.03
Dexmedetomidine	356 (51%)	72 (73%)	284 (47%)	**0.54**	220 (56%)	72 (73%)	148 (50%)	**0.48**
CICU Duration, d	14.0 (10.0, 22.0)	18.0 (12.5, 24.5)	14.0 (9.0, 22.0)	0.13	15.0 (10.0, 24.0)	18.0 (12.5, 24.5)	14.0 (9.0, 24.0)	0.08
Hospitalization duration, d	24.0 (16.0, 44.0)	31.0 (19.0, 50.5)	23.0 (15.0, 43.0)	0.12	26.0 (16.0, 44.0)	31.0 (19.0, 50.5)	24.0 (15.0, 41.0)	0.12
Survive to discharge	642 (91%)	90 (91%)	552 (91%)	0.02	353 (89%)	90 (91%)	263 (89%)	0.08
Seizures				0.05				0.01
Seizures	76 (11%)	12 (12%)	64 (11%)		49 (12%)	12 (12%)	37 (12%)	
No seizures	627 (89%)	87 (88%)	540 (89%)		347 (88%)	87 (88%)	260 (88%)	

RCP, Regional cerebral perfusion; *DHCA*, deep hypothermic circulatory arrest; *SMD*, standardized mean difference; *ECMO*, extracorporeal membrane oxygenation; *CICU*, cardiac intensive care unit. *n (%); Median (IQR). †SMDs ≥ 0.20 are bold to indicate imbalance between groups. ‡Patients may be in 2 or more categories. §Of the patients on a midazolam infusion, n = 6 with postoperative EEG seizures.

In our cohort, patients in the RCP group had longer CPB and aortic crossclamp times, consistent with previous studies from other institutions.[5,23] The reasons are likely multifactorial. RCP may provide a sense of security that the brain is being perfused, allowing for a greater perceived margin of safety and thereby less time urgency. In our cohort, the difference in support times may be due to differences in era and surgeon between the DHCA and RCP cohorts. Because increasing CPB time was associated with increasing seizure incidence (Figure E4), this may contribute to our negative findings. However, given that studies from other institutions have also demonstrated increasing CPB time with use of RCP, CPB time may be a component of the casual pathway between RCP and postoperative seizure occurrence. CPB flow rates and blood pressures achieved were not assessed in our study and are an area of future investigation. In our cohort, the median RCP duration of 49 minutes was longer than the median DHCA duration of 41 minutes, which is around the cut point after which the risk of neurologic injury is thought to increase.[24-26] This may also underlie the lack of difference in the incidence of postoperative seizures between the 2 groups. Additionally, of the patients who underwent RCP, 54% underwent some period of DHCA (median, 6 minutes; range, 1-21 minutes), which may have also impacted our findings.

Study Limitations

One notable limitation of this study is the vast majority of patients in the RCP cohort (96%) underwent surgery in the most recent era. Thus, there may have been changes over time that are not accounted for by propensity score matching. Notably, there have been changes to the surgical team over time, and thus our results may partly be due to unmeasured confounding. Additionally, although we did include STAT category in our propensity score matching, we did not directly parse out patients with cardiac lesions at the highest risk for developmental abnormalities (single ventricle physiology, d-transposition of the great arteries). Finally, the RCP group had a higher incidence of cardiac arrest in the operating room compared with the DHCA group, which may have confounded the findings.

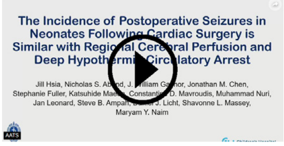
As a single-center study, these findings may not be generalizable to other institutions. Differences in RCP flow rates may result in different findings. Additionally, this study did not assess long-term outcomes, but rather assessed postoperative seizures as a surrogate for neurologic injury. Studies with long-term neurodevelopmental follow-up are needed to delineate the consequences each strategy may confer throughout the lifespan.

CONCLUSIONS

In this contemporary, single-center experience, the incidence of EEG seizures remains similar to previous years, and the incorporation of RCP was not associated with a lower incidence of seizures in comparison with DHCA. However, these findings may not be generalizable to other institutions due to variability in RCP technique, flow rates, and intraoperative neuromonitoring during RCP use. Additionally, our study did not adjust for all confounders, including changes in the surgical team over time, which may have impacted our findings. Given the conflicting data in the existing literature and paucity of adequately powered studies, prospective, multi-institutional studies are needed to determine whether RCP is a superior neuroprotective strategy to DHCA. However, there is the question of whether clinical equipoise exists among surgeons to conduct such a study. This begs the question if it is time to shift the focus away from perfusion strategies as a means of neuroprotection and to consider alternate modalities of optimizing neurodevelopment in this vulnerable population.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://www.aats.org/resources/the-incidence-of-post-operative-seizures-in-neonates-following-cardiac-surgery-is-similar-with-regional-cerebral-perfusion-and-deep-hypothermic-circulatory-arrest.



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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Key Words: deep hypothermic circulatory arrest, regional cerebral perfusion

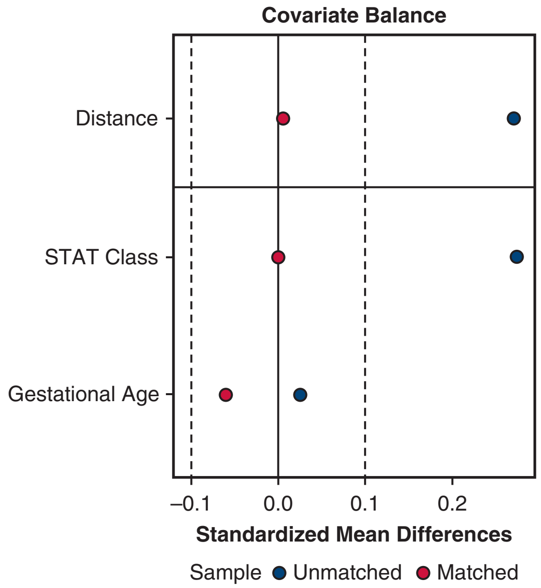

FIGURE E1. Love plot to assess covariable balance among matching variables. We used 3:1 nearest neighbor propensity score matching without replacement and a caliper of 0.2. The propensity score was estimated using logistic regression of the exposure (*RCP*) on the covariates gestational age and STAT class. After matching, SMDs for the matched covariates were below 0.1, indicating a successful match.

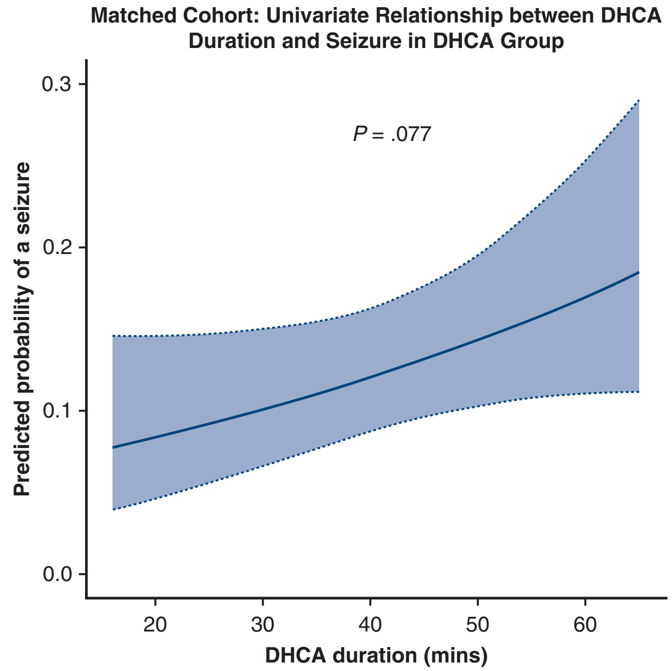

FIGURE E2. DHCA duration and predicted probability of seizure occurrence. *DHCA,* Deep hypothermic circulatory arrest.

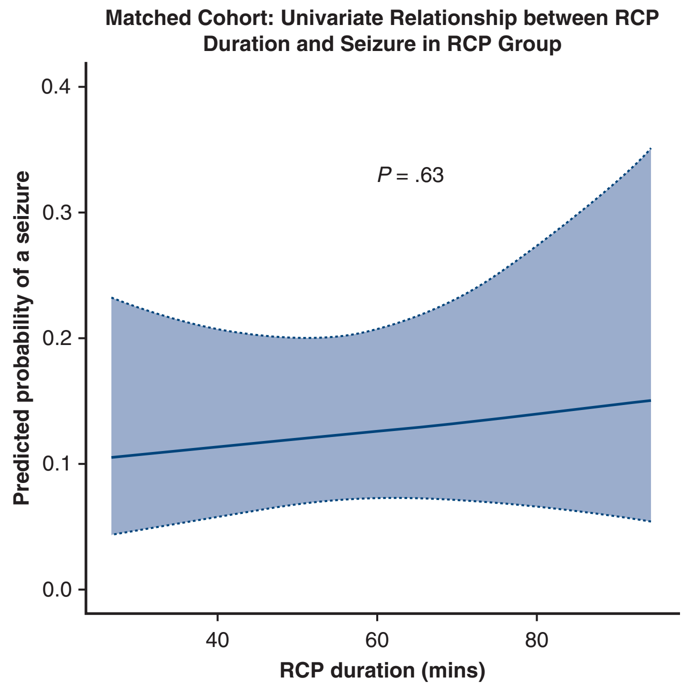

FIGURE E3. RCP duration and predicted probability of seizure incidence. *RCP,* Regional cerebral perfusion.

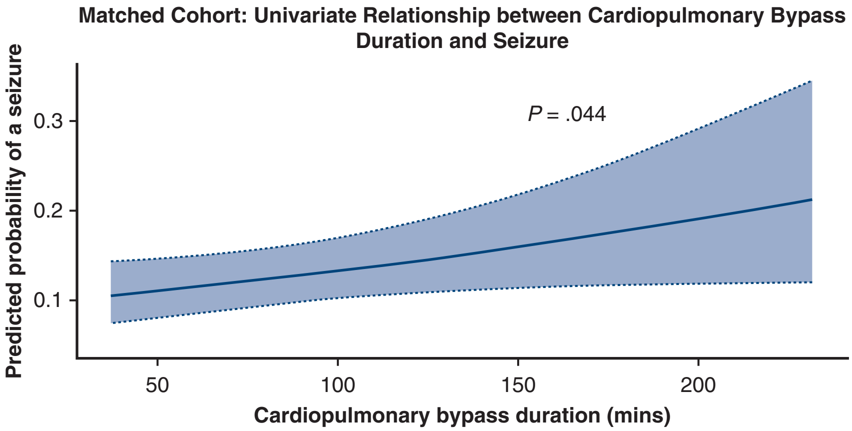

FIGURE E4. CPB duration and predicted probability of seizure occurrence.