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Neurodevelopmental Outcomes Following Regional Cerebral Perfusion with Neuromonitoring for Neonatal Aortic Arch Reconstruction

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Abstract

Background—In this study we report magnetic resonance imaging (MRI) brain injury, and 12 month neurodevelopmental outcomes, when regional cerebral perfusion (RCP) is utilized for neonatal aortic arch reconstruction.

Methods—Fifty seven neonates receiving RCP during aortic arch reconstruction were enrolled in a prospective outcome study. RCP flows were determined by near-infrared spectroscopy and transcranial Doppler monitoring. Brain MRI were performed preoperatively and 7 days postoperatively. Bayley Scales of Infant Development III was performed at 12 months.

Results—Mean RCP time was 71 ± 28 minutes (range 5–121), mean flow 56.6 ± 10.6 ml/kg/min. New postoperative MRI brain injury was seen in 40% of patients. For 35 RCP patients at age 12 months, mean Bayley III composite standard scores were: Cognitive = 100.1 ± 14.6,(range 75–125); Language = 87.2 ± 15.0, (range 62–132); Motor = 87.9 ± 16.8, (range 58–121).Increasing duration of RCP was not associated with adverse neurodevelopmental outcomes.

Conclusions—Neonatal aortic arch repair with RCP utilizing a neuromonitoring strategy results in 12-month cognitive outcomes that are at reference population norms; language and motor outcomes are lower than the reference population norms by 0.8–0.9 standard deviation. This largest RCP group with neurodevelopmental outcomes published to date demonstrates that this technique is effective and safe in supporting the brain during neonatal aortic arch reconstruction.

Keywords

Anesthesia; brain; cardiopulmonary bypass (CPB); CHD; hypoplastic left heart syndrome; neurocognitive deficits

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Introduction

Over the past decade, studies of long term neurodevelopmental outcomes after complex neonatal cardiac surgery have demonstrated a high incidence of neurodevelopmental abnormalities, with up to half of infants going on to demonstrate long term delays on tests of cognitive and motor function.[1] Modifiable perioperative factors, including cardiopulmonary bypass (CPB) techniques, have been an important area of inquiry, with prolonged deep hypothermic circulatory arrest (DHCA) assumed to be an important contributing factor to brain injury.[2] Neonates with hypoplastic left heart syndrome (HLHS) undergoing aortic arch reconstruction with the Norwood Stage I palliation are at particularly high risk, with these patients consistently scoring lower in tests of neurodevelopmental function at age 1 to 5 years, than patients with other diagnoses such as D-transposition of the great arteries. Motor performance is particularly adversely affected in the first years after neonatal surgery. [3,4]

Regional cerebral perfusion (RCP), also termed antegrade cerebral perfusion, or regional low flow cerebral perfusion, was described over a decade ago as a cerebral support technique for neonatal aortic arch reconstruction. [5,6] This technique provides antegrade cerebral blood flow by perfusing the brain only via a graft sutured to the innominate artery or small arterial cannula advanced cephalad into the innominate artery. Perceived advantages of RCP include maintaining oxygenation and blood flow to the brain, avoiding long periods of DHCA, and allowing more time to complete the arch repair.[7,8] Despite the intuitive appeal of this technique, previous comparison studies have not demonstrated superior long term neurodevelopmental outcomes with RCP vs. DHCA; in fact neurodevelopmental outcomes 1 yr after Norwood Stage I palliation with RCP are significantly below population norms.[9,10] There remains disagreement among surgeons as to which technique is preferred, as well as divergent practice, with a significant proportion of surgeons utilizing each method.[11]

Our group has previously described an RCP technique utilizing neurological monitoring with near infrared spectroscopy, and transcranial Doppler ultrasound, to adjust flow rates during RCP to standardize cerebral oxygen delivery for the individual patient.[12] This technique results in significantly higher RCP flow rates of 40–80 ml/kg/min, compared with 20–30 ml/kg/min typically described. [7,10] We also demonstrated adequate oxygenation to the contralateral cerebral hemisphere using this method.[13] In a cohort of 43 patients undergoing RCP, pre- and postoperative MRI studies demonstrated no immediate adverse effects of RCP with regard to rate, classification, or location of brain injury when compared to patients undergoing standard CPB techniques.[14] We also demonstrated a low rate of seizures in the perioperative period diagnosed by electroencephalography, with only a single RCP patient (2.3%) experiencing 2 brief seizures.[15]

The purpose of this study was to prospectively evaluate a cohort of neonates undergoing aortic arch reconstruction using RCP, to assess neurodevelopmental outcomes at age 12 months. We also sought to determine important associations with these outcomes, including patient and perioperative factors, and other clinical events during the first year of life.

Patients and Methods

This study was approved by the Baylor College of Medicine Institutional Review Board, and patients were enrolled after signed informed consent was obtained from parents. It was a prospective, observational study with a single patient cohort receiving uniform CPB and perioperative treatment protocols. Neonates (<30 days of age) undergoing RCP for aortic arch reconstruction were eligible for enrollment. Single ventricle and two ventricle lesions were included. Exclusion criteria were gestational age less than 35 weeks at birth, weight

less than 2.0 kg, recognizable dysmorphic syndrome, or preoperative cardiac arrest for greater than 3 minutes.

CPB technique consisted of a 3.5 mm polytetrafluoroethylene graft sutured to the right innominate artery as arterial inflow, with bicaval or single atrial cannulation. CPB flow rates of 150 ml/kg/min were used at all times, except for periods of DHCA, or RCP. [12] CPB flow during RCP was adjusted to maintain mean cerebral blood flow velocity in cm/sec, measured with transcranial Doppler, to within 10% of full CPB baseline. Bilateral regional cerebral oxygen saturation (rSO_2) was measured and right sided rSO_2 maintained >90% during RCP, as described previously. (INVOS 5100B, Somanetics, Inc., Troy, MI). [12] If the rSO_2 was less than 50% before or after bypass, attempts were made to increase oxygen delivery to the brain, or decrease oxygen consumption, as described previously.[14] Mean rSO_2, and area under the curve for rSO_2 <45% were calculated for the preoperative, intraoperative, and 72 hour postoperative periods, as [rSO_2 <45% × minutes]. (Excel, Microsoft Corp, Redmond WA)[16]

Mean arterial pressure was maintained at 30–35 mm Hg, facilitated with α-receptor blockade with phenoxybenzamine or phentolamine. Aortic arch reconstruction with RCP was performed at 18° C, with cooling accomplished over no less than 20 minutes. pH stat blood gas management was used throughout CPB. One dose of methylpredisolone, 20 mg/kg, was given in the CPB prime. Aprotinin was utilized for the first 30 cases; the last 27 cases utilized ε-aminocaproic acid. Hematocrit was maintained at 30–35% during cooling and hypothermic periods, and increased to 40–45% during rewarming. Conventional ultrafiltration was utilized throughout the CPB period; post-CPB modified ultrafiltration was not used.

Doses of anesthetic, analgesic, and sedative drugs were recorded for the intraoperative period, and first 72 hours of the intensive care unit course. Anesthetic gas exposure was quantified as minimum alveolar concentration-hours (MAC-hours) of isoflurane, with neonatal MAC 1.6%, calculated in 15-min time increments. Doses of morphine were converted into fentanyl equivalents using a 100:1 conversion factor, and added to fentanyl dose. Doses of midazolam and lorazepam, in mg/kg, were added to calculate benzodiazepine exposure. No other sedative or analgesic drugs were administered in the first 72 postoperative hours. Chromosome analysis was performed by chromosomal microarray, or fluorescence in situ hybridization analysis, when a genetic syndrome was suspected. Medical records were reviewed for the number of subsequent anesthetics after the neonatal surgery, in the first 12 months, including cardiac and non-cardiac anesthetics. Records were also reviewed for cardiac arrest, extracorporeal membrane oxygenation cannulation, and deaths. In addition, intraoperative doses of volatile anesthetic agents, midazolam, and fentanyl were quantified for all subsequent anesthetic exposures in the first 12 months.

Brain MRI under general endotracheal anesthesia was obtained immediately before surgery. MR imaging was performed on a 1.5 Tesla Intera scanner (Philips Medical Systems, Best, the Netherlands), including standard T1, T2, diffusion weighted imaging, and susceptibility weighted imaging. [14] Postoperative MRI was obtained when the patient was clinically stable, at 7–10 days postoperatively. All MRI were evaluated by pediatric neuroradiologists unaware of diagnosis or surgery. Abnormalities were classified as: white matter injury, intraparenchymal infarction, or intraparenchymal or intraventricular hemorrhage. [14]

The Bayley Scales of Infant and Toddler Development, Third Edition (PsychCorp.-Harcourt, Brace, & Co., San Antonio TX, 2006) was performed at 12 months of age. The Bayley III consists of three primary composite standard scores, the Cognitive, Motor, and Language Composite scores, measured by performance of specified tasks, scored against a normative

population, and scaled to have a mean score of 100 with standard deviation of 15. In addition, a parental questionnaire is administered, and Social-Emotional and Adaptive Behavior Composite Scores are derived. These tests were administered by a single developmental psychologist unaware of diagnosis or surgery performed. Maternal intelligence was evaluated using the Weschler Abbreviated Scale of Intelligence. (PsychCorp.-Harcourt, Brace, & Co., San Antonio TX, 1999).

Statistical Analysis—The RCP group was divided into single ventricle palliations, and complete two ventricle repairs, for comparison of patient and demographic factors and outcomes. Normally distributed data are reported as mean ± SD; non- normally distributed data (Shapiro-Wilk test $p<0.05$) reported as median (25^{th}–75^{th} percentile). Data were analyzed using two sided T test, Mann-Whitney Signed Rank Test, Fisher Exact Test or χ-square analysis as appropriate. Primary outcomes were the Cognitive, Language, and Motor Composite Standard Scores of the Bayley Scales III. To determine associations with primary outcomes, a best subsets multivariable linear regression analysis was performed on 17 covariates. The model with the lowest Mallow's Cp Statistic was chosen, and covariates with p values <0.05 and 95% confidence interval excluding zero were included in the final model. (Stata 10, Stata Corp., College Station TX).

Results

Fifty-seven patients were enrolled in the study between November 2005 and December 2010. Ten patients, all with HLHS or a variant who underwent Stage I palliation with systemic-to-pulmonary shunt, died after the initial surgical period; 9 before bidirectional cavopulmonary anastomosis, and one after this procedure. The patient characteristics and preoperative data are reported in Table 1. Mean RCP flow rate was 56.6 ± 10.6 ml/kg/min, (range 35 to 81 ml/kg/min), and mean RCP time was 71 ± 28 minutes (range 5 to 121 minutes). Intraoperative data are reported in Table 2. Postoperative data are presented in Table 3.

Pre- and postoperative MRI findings are reported in Table 4. Twelve of the 23 new postoperative MRI brain injuries included white matter injury; 70% of these injuries were minimal in severity, without differences between groups. New lesions were equally distributed between cerebral hemispheres, and none of the new lesions was judged to be secondary to excessive cerebral blood flow during RCP.

Thirty five patients (74% of survivors) returned for 12 month Bayley Scales of Infant Development III assessment. The mean composite standard scores for all 35 patients were: Cognitive = 100.1 ± 14.6 (range 75–125); Language = 87.2 ± 15.0 (range 62–132), Motor = 87.9 ± 16.8 (range 58–121). There were no differences in the three primary outcome scores between single and two ventricle groups. (Table 5)

Final models for best subsets multivariable regression analysis are reported in Table 6. Lower maternal intelligence, longer intensive care unit length of stay, higher benzodiazepine dose, and longer DHCA times were associated with lower cognitive scores. Longer RCP time was associated with higher cognitive scores. For both language and motor scores, presence of a chromosome anomaly, and lower maternal intelligence were associated with lower scores. Higher benzodiazepine dose was associated with lower language scores. The use of aprotinin and larger total number of general anesthetics in the first 12 months were associated with lower motor scores.

Comment

The primary new finding of our study is that RCP as a cerebral support technique for neonatal arch reconstruction, using our protocol to standardize oxygen delivery to the brain, results in cognitive outcomes at age 12 months that are equal to the reference population mean for the Bayley Scales III. Language and motor outcomes are lower than the reference population mean by 0.8–0.9 standard deviation for RCP patients. This group of 35 patients receiving RCP is the largest published to date evaluated with neurodevelopmental follow-up at 12 months.

We have demonstrated some novel and important associations with 12 month outcomes after adjusting for potential confounding factors, following neonatal cardiac surgery employing RCP. First, the duration of RCP itself was not associated with adverse outcomes; in fact longer RCP was associated with improved cognitive score. This suggests that RCP, even when prolonged, is a safe and effective technique for cerebral support during neonatal arch reconstruction. Second, anesthetic and sedative technique, both in the perioperative period, and during the subsequent intensive care unit course and anesthetics during the first 12 months, may have an important effect on outcome. Benzodiazepines, which worsened outcomes with higher doses, bind to γ-aminobutryic acid receptors in the brain to produce their sedative effects and cause neuroapoptosis in neonatal animal models.[17] In addition, greater number of subsequent general anesthetic exposures was associated with lower neurodevelopmental scores. Repeated or prolonged anesthetic exposures have also been associated with neurodevelopmental problems in some human retrospective studies. [18] Further study of anesthetic and sedative techniques and doses is required to determine whether approaches can be modified to potentially improve outcomes. Aprotinin was associated with lower motor scores; this agent is no longer available in the U.S. Finally, the non-modifiable factors of chromosome anomaly and maternal intelligence were strongly associated with 12 month neurodevelopmental outcomes.

We also tested several factors that were not associated with neurodevelopmental outcomes in this cohort of patients. Among these was rSO_2, either mean values, or area under the curve of rSO_2 <45%. Many single ventricle patients experience significant degree and duration of cerebral desaturation postoperatively, yet this factor was not associated with outcomes. Potential reported causes of cerebral desaturation in the early postoperative period include low cardiac output, and loss of cerebral autoregulation after deep hypothermic bypass.[19,20] MRI brain injury, either before or after surgery, also was not associated with 12 month Bayley III scores in this analysis. Previous studies report a 20–40% incidence of preoperative MRI brain injury, and a 35–75% incidence of new postoperative brain injury in neonatal cardiac surgery patients.[14,16,21,22] Our 40% incidence of new MRI brain injury after RCP compares with the 73% incidence after RCP reported by Dent et al. [16] Cerebral oxygen saturation, autoregulation, and MRI injury deserve further study in larger patient cohorts to determine their predictive value for longer term neurodevelopmental problems.

Our study is the first to report neurodevelopmental outcomes with RCP using the Bayley Scales III, which is the newest and most comprehensive version of the infant neurodevelopmental assessment tool used most commonly after infant cardiac surgery.[24] Because of significant differences in this test compared to the earlier Bayley Scales of Infant Development II, direct comparison to earlier infant cohorts undergoing RCP is difficult, but these earlier reports do offer some insight. Goldberg et al, performed a prospective, randomized, controlled trial, of RCP vs. DHCA for the Norwood stage I palliation in 77 HLHS patients.[10] At one year, the 22 surviving RCP patients had a Bayley II Mental Development Index of 88.9 ± 21.6. Psychomotor Development Index mean was 74.0 ± 20.

The major differences in technique for RCP in their study were that α-stat pH management was utilized, RCP flows were 20 ml/kg/min and did not vary, and near infrared cerebral oximetry was not used to guide RCP flow rates. The mean RCP time was 41.0 ± 9.0 minutes. Visconti et al performed a retrospective analysis of 29 patients undergoing either Norwood Stage I palliation, or single ventricle palliation with aortic arch reconstruction, 9 received RCP as a primary strategy, and 20 had DHCA as a primary strategy.[9] pH stat strategy, and RCP flows of 30–40 ml/kg/min were utilized, without neurological monitoring. The RCP times are not reported. Mean Mental Development Index on the Bayley II for the RCP patients was 88.0 ± 12.1, and Psychomotor Development Index was 75.5 ± 15.1. Neither of these studies reported an outcome difference with RCP vs. DHCA for arch reconstruction.

Limitations

This study is limited by several important factors, the most significant of which is the small sample size evaluated for neurodevelopmental outcomes, thus potentially limiting the conclusions of this study. Nonetheless, ours is the largest single center study to date to report neurodevelopmental outcomes with RCP. This study was not a controlled trial of RCP vs. DHCA, and thus conclusive statements about the superiority of one technique vs. another cannot be made from this data.

Conclusions

In this study we have demonstrated that RCP, guided by neuromonitoring to standardize flow rates during neonatal aortic arch reconstruction, results in neurodevelopmental outcome at age 12 months that is at reference population norms for cognitive performance on the Bayley III, and 0.8–0.9 standard deviation below reference population means for language and motor performance. This largest RCP group with neurodevelopmental outcomes published to date demonstrates that this technique is effective and safe in supporting the brain during neonatal aortic arch reconstruction.

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Table 1

Preoperative Patient Characteristics, n=57

Parameter	Single Ventricle, n=47	Two Ventricle, n=10	P value
Diagnosis (n,%)	HLHS, n=42 Double inlet left ventricle, arch obstruction, n=2 Tricuspid atresia, arch obstruction, n=2 Double outlet right ventricle, mitral atresia, arch obstruction, n=1	VSD with arch obstruction, n=7 Dextrotransposition with arch obstruction, n=3	NA
Birthweight (g)	3091 ± 391	3125 ± 486	0.814
Gestational Age (Weeks)	38.6 (38.0–39.3)	38.6 (37.0–39.0)	0.666
Head Circumference (cm)	33.4 ± 1.5	33.7 ± 1.2	0.590
Age at Surgery (Days)	7 (5–9)	7(4–10)	0.824
1 min Apgar Score	8 (8–9)	8 (8–9)	0.831
5 min Apgar Score	9 (8–9)	9 (8–9)	0.659
Chromosomal abnormality (n,%)	7 (15)	4 (40)	0.088
Mean rSO_2 (%)	61.2 (55.9–65.3)	72.9 (64.5–78.6)	0.002 *
rSO_2c <45% AUC (%-min)	0.0 (0.0–28.6)	0.0 (0.0–0.0)	0.298

AUC, area under the curve; HLHS, hypoplastic left heart syndrome; RCP, regional cerebral perfusion; rSO_2, regional cerebral oxygen saturation; VSD, ventricular septal defect. Data expressed as mean ± standard deviation, or median (25^{th}–75^{th} percentile).

* $p \leq 0.05$.

Table 2

Intraoperative and Surgical Repair Data, n=57

Parameter	Single Ventricle, n=47	Two Ventricle, n=10	P value
Surgical Repair, n (%)	Norwood stage I palliation, n=42 Aortic arch reconstruction, PA banding, n=3 Aortic arch reconstruction, palliative arterial switch operation, n=2	VSD, aortic arch reconstruction, n=7 Arterial switch operation, aortic arch reconstruction, n=3	NA
CPB Time, min	193 (169–234)	155 (144–295)	0.123
Aortic Crossclamp Time, min	97 (83–108)	96 (85–176)	0.482
DHCA Time, min	11 (8–14) (n=41)	15 (15–16)(n=2)	0.182
RCP Time, min	80.3 ± 20.1	25.9 ± 14.6	<0.001 *
Lowest Temperature, °C	17.5 (17.3–17.9)	17.9 (17.6–18.0)	0.051
rSO_2 <45% AUC (%-min)	62.1 (0.1–480.0)	0.0 (0.0–1.0)	0.005
rSO_2 mean (%)	69.6 (64.7–72.7)	77.3 (75.3–83.4)	<0.001 *
Fentanyl dose (mcg/kg)	195 (157–306)	171 (112–190)	0.116
Midazolam dose (mg/kg)	1.22 (0.83–1.5)	1.07 (0.83–1.30)	0.361
Isoflurane MAC-hours	1.25 (0.79–2.00)	1.45 (0.67–2.80)	0.578

AUC, area under the curve, MAC-hours, minimum alveolar concentration × hours, CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest; RCP, regional cerebral perfusion; rSO_2, regional cerebral oxygen saturation. Data expressed as mean ± standard deviation, or median (25^{th}–75^{th} percentile).

* $p \leq 0.05$.

Table 3

Postoperative Data, n=57

Parameter	Single Ventricle, n=47	Two Ventricle, n=10	P value
rSO_2 <45% AUC (%-min)	257 (4–2003)	0 (0–0)	<0.001
rSO_2 mean (%)	57.8 ± 6.1	76.1 ± 5.1	<0.001
Cardiac arrest, n(%)	2 (4)	0	1
Extracorporeal membrane oxygenation, n(%)	2 (4)	0	1
Mechanical ventilation days	4 (4–7)	4 (3–5)	0.262
Fentanyl equivalents, 1st 72 h (mcg/kg)	80 (46–157)	24 (18–94)	0.041
Benzodiazepine dose, 1st 72 h (mg/kg)	2.15 (0.33–6.09)	0.81 (0.04–1.60)	0.145
Intensive care unit length of stay (days)	9 (7–16)	8 (7–8)	0.151
Hospital length of stay (days)	34 (24–54)	26 (22–37)	0.123
Hospital discharge mortality (n,%)	2 (4)	0	1
Mortality, 1st 12 months (n,%)	10 (21)	0	0.183

AUC, area under the curve; RCP, regional cerebral perfusion; rSO_2; regional cerebral oxygen saturation. Data expressed as mean ± standard deviation, or median (25^{th}–75^{th} percentile).

* $p \leq 0.05$.

Table 4

Brain Magnetic Resonance Imaging Data, n=57

MRI Findings	Single Ventricle, n=47	Two Ventricle, n=10	P value
Preoperative MRI brain injury, n(%)	14 (30)	2 (20)	0.708
NEW 7-day Postoperative MRI brain injury, n(%)	21 (45)	2 (20)	0.178

RCP, regional cerebral perfusion; Brain injury definition: total number of patients with white matter injury, and/or intraparenchymal infarction, and/or intraparenchymal or intraventricular hemorrhage added together.

Table 5

12 Month Bayley Scales of Infant and Toddler Development III Neurodevelopmental Outcome Data and Maternal Intelligence, n=35

Domain	Single Ventricle, n= 27	Two Ventricle, n=8	P value
Cognitive	99.3 ± 13.2	103.1 ± 19.4	0.520
Language	87.6 ± 12.9	85.9 ± 21.6	0.781
Motor	87.9 ± 15.7	88.0 ± 21.4	0.987
Social-Emotional	100 (91–105)	90 (73–99)	0.05 *
Adaptive Behavior Scale: General Adaptive Composite	90.7 ± 15.7	88.4 ± 14.7	0.732
Conceptual	96.9 ± 15.4	93.9 ± 15.1	0.649
Social	93.3 ± 15.4	93.9 ± 15.1	0.927
Practical	88.1 ± 12.4	85.7 ± 11.2	0.642
Maternal Intelligence	102.8 ± 16.0	101.0 ± 11.7	0.784

Data expressed as mean ± standard deviation, or median (25^{th}–75^{th} percentile).

* $p \leq 0.05$.

Table 6

Best Subsets Multivariable Regression Final Model, n=35

Variable	Cognitive Score		Language Score		Motor Score	
	P value	Coefficient, 95% CI	P value	Coefficient, 95% CI	P value	Coefficient, 95% CI
RCP time	0.007	0.28 (0.08 to 0.48)	NA	NA	NA	NA
DHCA time	<0.001	−0.83 (−1.28 to −0.37)	NA	NA	NA	NA
CPB time	NA	NA	0.007	0.08 (0.01 to 0.15)	NA	NA
Aprotinin use	NA	NA	NA	NA	0.05	−9.13 (−18.08 to −0.18)
Intensive care unit length of stay	0.045	−0.14 (−0.27 to −0.01)	NA	NA	NA	NA
Total number general anesthetics, first 12 months	NA	NA	NA	NA	0.033	−2.16 (−4.13 to −0.19)
Fentanyl 1st	NA	NA	0.00	0.029	NA	NA
12 months			7	(0.01 to 0.050)		
Benzodiazepi ne equivalents 1st 12 months	0.049	−3.87 (−7.72 to −0.02)	0.002	−7.86 (−12.53 to −3.20)	NA	NA
Chromosome anomaly	NA	NA	0.009	−13.50 (−23.41 to −3.59)	0.036	−12.90 (−25.06 to −0.92)
Maternal Intelligence Quotient	<0.001	0.45 (0.20 to 0.69)	<0.001	0.49 (0.24 to 0.73)	0.002	0.49 (0.19 to 0.79)

Abbreviations: CI, confidence interval; CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest; rSO_2, regional cerebral oxygen saturation.