Usefulness of Deep Hypothermic Circulatory Arrest and Regional Cerebral Perfusion in Children

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To compare the safety and usefulness of deep hypothermic circulatory arrest (DHCA) and regional cerebral perfusion (RCP) during pediatric open heart surgery. Between January 1, 2004 and September 30, 2012, 1250 children with congenital cardiac defect underwent corrective operation with the DHCA or RCP technique in the Shanghai Children's Medical Center. Of them, 947 cases underwent the operation with the aid of DHCA (DHCA group), and 303 cases with RCP (RCP group). The mean DHCA time was 30.64 ± 15.81 (7–63) minutes and mean RCP time was 36.18 ± 12.86 (10–82) minutes. The mortality rate was 7.18% (68/947) and 6.60% (20/30) in two groups, respectively. The postoperative incidences of temporary and permanent neurological dysfunction were 6.23% (59/947) in the DHCA group and 2.64% (8/303) in the RCP group ($p < 0.01$). The incidence of other complications such as low cardiac output, renal dysfunction, and lung issues are similar in both groups. RCP is a reliable technique for cerebral protection and it facilitates time-consuming corrected procedures for complex congenital cardiac defect repair procedures.

Introduction

SINCE THE INTRODUCTION of deep hypothermic circulatory arrest (DHCA) in the early 1960s, it has been increasingly used in centers with expertise in open heart surgery for infants, children, and adults. The use of this technique is based on the premise that there is a safe duration of total circulatory arrest that is inversely related to the body temperature (Kirkin and Barratt-Boyes, 1993). However, this procedure has been linked with neurologic sequelae. Although the duration of safe DHCA remains unknown, adverse outcomes are more frequently observed in children with a DHCA duration exceeding 45 minutes (Newburger *et al.*, 1993). Various strategies, including antegrade and retrograde cerebral perfusion are used for preventing neurological problems and allowing the surgeons more time for optimal repair and hemostasis has been developed (Griep, 2001; Lee *et al.*, 2011; Pacini *et al.*, 2012; Senanayake *et al.*, 2012). Regional cerebral perfusion (RCP), also called antegrade cerebral perfusion is one of the most promising cerebral protection techniques and is dominantly used in children (Hofer *et al.*, 2005; Algra *et al.*, 2012; Pacini *et al.*, 2012; Senanayake *et al.*, 2012). RCP has been the cerebral protection method of choice in the Shanghai Children's Medical Center since 2004. The aim of the present study was to compare the safety and usefulness of DHCA and RCP during pediatric open heart surgery.

Materials and Methods

Patients

We reviewed the records of 1250 consecutive patients who underwent operations with DHCA and RCP congenital cardiac surgery between January 1, 2004 and September 30, 2012. The clinical characteristics of these patients are listed in (Table 1). Of them, 947 cases underwent the operation with the aid of DHCA, and 303 cases with RCP. In addition, the number of cases operated in each year is listed in (Table 2).

Anesthesia

All patients were premedicated with oral midazolam 0.5 mg/kg. Anesthesia was induced with midazolam 0.1 mg/kg, sufentail 2.0 (g/kg, rocuronium 0.6 mg/kg at the discretion of the anesthesiologist. Anesthesia was maintained in every case with oxygen-enriched air (if needed) and sufentail, and pancuronium. Midazolam, sufentail, and rocuronium doses represented the total amount administered during the surgery. Additional volatile anesthetic (isoflurane or sevoflurane) was administered at the discretion of the anesthesiologist caring for the patient, but it was administered to nearly every patient. All patients underwent povidone-iodine preparation of the skin before surgery. Heparin 200 U/kg was administered before cardiopulmonary bypass (CPB).

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TABLE 1. CHARACTERISTICS OF PATIENTS UNDERGOING OPERATION WITH DEEP HYPOTHERMIC CIRCULATORY ARREST OR REGIONAL CEREBRAL PERFUSION

	DHCA group (n=947)	RCP group (n=303)
Age (month)	1.305±0.982 (3 days–170 month)	0.803±0.532 (4 days–61 month)
Gender (m/f)	642/305	216/87
Weight (kg)	6.795±3.761 (2.6–38)	5.341±3.052 (2.7–31)
Diagnosis		
CoA with ASD/VSD/ CAVC	485	139
DORV	67	24
IAA	156	58
PA	79	19
TAPVC	30	7
TGA	96	37
Others	34	19

DHCA, deep hypothermic circulatory arrest; RCP, regional cerebral perfusion; CoA, coarctation of the aorta; ASD, atrial septal defect; VSD, ventricular septal defect; CAVC, complete atrioventricular canal; DORV, double outlet of the right ventricle; IAA, interrupted aortic arch; PA, pulmonary atresia; TAPVC, total anomalous pulmonary venous connection; TGA, transposition of the great arteries.

Additional heparin was given as needed to maintain the activated clotting time >400 seconds before CPB.

Surgery and cardiopulmonary bypass

Operations were performed through a median sternotomy in all cases. As for the site of arterial cannulation for CPB, the ascending aorta was used for all cases, and in IAA cases, a second aortic cannula is connected to the arterial tubing by a Y connector and inserted in the main pulmonary artery. Venous cannulation was routine with bicaval or single atrial cannulation, depending on the anomalies. During CPB, roller pumps (Sarns 8000, Stockert III, and Terumo System I) and a nonpulsatile pump flow with a membrane oxygenator (Minimax Puls, Medtronic, Lilliput 901, 902; Dideco) were maintained. CPB was performed after priming a membrane oxygenator with 450–800 mL of fluid and blood products. The priming formula has been described previously to maintain

the hematocrit at 22%–25% in children and 25%–28% in neonates and infants (Zhu *et al.*, 2006). During CPB, the flow rate was kept from 2.2 to 2.8 L/(m²·minute), according to the age and size (the younger the patient, the higher the flow rate), except for periods of DHCA or RCP. Activated clotting time (Hemochron Jr. II; Edison ITC) and blood gases were checked every 20 minutes during bypass. Activated clotting time was maintained for more than 480 seconds, and potassium, calcium, and 5% sodium bicarbonate were used if necessary. Blood cardioplegia was used and the formula of the blood cardioplegia was the same as the del Nido formula. Ultrafiltrators were set up for every child weighing less than 10 kg. Conventional ultrafiltration and modified ultrafiltration were used for every patient. Because of the financial limitation, no extracorporeal membrane oxygenation was used in these patients. During cooling, mixed gas of 5% CO₂ and 95% O₂ was used to flush the oxygenator to maintain the pH stat. All patients were cooled by maintaining a 10°C gradient between arterial blood and rectal temperature. When the patient was cooled to a rectal temperature of 18°C–20°C, the circulatory arrest or RCP was initiated with the aortic clamping. In the RCP group, the temperature of the perfusate for RCP was set at 18°C. RCP with oxygenated blood was performed through an aortic cannula, which was inserted in the right innominate artery after aortic clamping. RCP was then started at the rate of 10 mL/(kg·minute), then slowly increased to 40–50 mL/(kg·minute) with a pressure of 30–40 mm Hg. During RCP, the flow is provided to the brain through the right innominate and right vertebral arteries (arising from the base of the right subclavian artery, which is above the snare). Neuromonitoring was not used during the procedure. After the main procedure was finished, DHCA and RCP were stopped and the circulation was recovered as soon as possible. Rewarming was initiated with a 10°C gradient between arterial blood and rectal temperature. In addition, the water temperature did not exceed 40°C.

Mortality and morbidity

Early postoperative mortality and morbidity, which included neurological complications, low cardiac output, renal dysfunction, and lung complications, were recorded. All patients who died intraoperatively or during the first 24 hours after the operation without an opportunity for adequate evaluation of their neurologic status were excluded from the neurological assessment. Formal psychometric studies or computed tomographic scanning or magnetic resonance imaging of the brain was not performed. Neurological disorders, such as coma, seizure, athetosis, and irritability, were recorded. Low cardiac output status was clinically defined as the inotrope score, which is the dopamine dose (μg/(kg·minute))+dobutamine dose (μg/(kg·minute))+100×epinephrine dose (μg/(kg·minute)), more than 20. Renal dysfunction was defined as the urine output less than 1 mL/(kg·hour), and the patients affected with renal dysfunction were treated with peritoneal dialysis. Lung issues included infection, atelectasis, pulmonary hypertension, bronchus spasm, pneumothorax, and hydrothorax.

Statistical methods

Medical records of all 1250 cases operated with DHCA or RCP were reviewed. Postoperative complications that

TABLE 2. NUMBER OF THE PATIENTS IN EACH YEAR

Year	DHCA cases	RCP cases
2004	95	21
2005	142	19
2006	168	44
2007	85	22
2008	65	25
2009	124	41
2010	86	34
2011	120	66
2012.1–9	62	31
Total	947	303

TABLE 3. MORTALITIES AND MORBIDITIES POSTOPERATIVELY

	DHCA group (n=947)	RCP group (n=303)	p-Value
CPB time	104.33±37.96 (50–242)	136.19±42.26 (65–237)	<0.01
Aortic clamping time	57.95±15.81 (21–160)	72.84±42.49 (18–156)	>0.05
DHCA/RCP time	30.64±15.81 (7–63)	33.18±12.86 (10–82)	>0.05
The ventilator tube time (hour)	64.72±35.26 (24–196)	71.13±42.28 (24–192)	>0.05
ICU time	5.90±3.90 (0–21)	5.65±3.00 (0–22)	>0.05
Mortality rate	7.18% (68/947)	6.60% (20/303)	>0.05
Low cardiac output	27.0% (256)	30.3% (92)	>0.05
Neurological complication	6.23% (59)	2.64% (8)	<0.01
Renal dysfunction	9.82% (93)	10.56% (32)	>0.05
Lung complications	18.16% (172)	21.12% (64)	>0.05

CPB, cardiopulmonary bypass.

occurred before discharging were recorded. SPSS application software version 11.0 (SPSS, Inc.) was used for statistical analyses. Significant differences between two groups were assessed with univariate analysis: categorical data were compared by means of the χ^2 test and continuous variables with the Student's *t*-test.

Results

Totally, 19,937 cases underwent open heart surgery with CPB in the Shanghai Children's Medical Center between January 1, 2004 and September 30, 2012. Of them, 6.27% (1250/19,937) cases underwent operation with DHCA or RCP. The bypass time was 104.33±37.96 (50–242) minutes in the DHCA group and 136.19±42.26 (65–237) minutes in the RCP group ($p<0.01$). However, because the circulatory arrest time was not added into the bypass time, the real time from the bypass start to the end was about 135 minutes, which was similar to the RCP group. The DHCA time and RCP time in two groups were 30.64±15.81 (7–63) minutes and 33.18±12.86 (10–92) minutes, respectively. The mean RCP flow rate was 46.57±12.35 mL/(kg·minute), [range, 35–60 mL/(kg·minute)] (Table 2).

Mortalities and morbidities

Mortality rates and complications are listed in Table 2. The overall hospital mortalities were 7.18% in the DHCA group and 6.60% in the RCP group. Postoperative outcome data showed no significant differences in the mortality rates in the patients who have been operated with or without RCP. Most postoperative death resulted from cardiac dysfunction.

Neurological events postoperatively were reported in 59 patients in the DHCA group and 8 patients in the RCP group. A significantly higher incidence of neurological events was found in the DHCA group (6.23%) in comparison to the RCP group (2.64%) ($p<0.01$) (Table 2).

Low cardiac output, lung issues, and renal dysfunction were the first three most frequent complications after open heart surgery. The incidence of these complications was not significantly different between the two groups (Table 3).

Discussion

Circulatory arrest during cardiac surgery is associated with a greater risk of postoperative neurologic abnormalities

(Newburger *et al.*, 1993; Bellinger *et al.*, 1995). The cerebral protection methods currently used for aortic surgery and complex open heart surgery are profound hypothermic circulatory arrest with or without retrograde cerebral perfusion, and antegrade RCP (Hofer *et al.*, 2005; Lee *et al.*, 2011; Algra *et al.*, 2012; Pacini *et al.*, 2012; Senanayake *et al.*, 2012). Each technique has its own advantages and disadvantages. The impact of DHCA and RCP on the organ function in patients undergoing open heart surgery is of increasing interest. In recent years, the DHCA technique was used in 947 patients and cold-induced reduction in the cerebral metabolic rate is a well-known mechanism for protection against anoxic and ischemic insults (Steen *et al.*, 1983). Indeed, systemic hypothermia decreases the cerebral metabolic rate for oxygen by reduction of 6%–7% per degree celsius temperature. Ehrlich *et al.* (2002) reported in pig brains that the metabolism was reduced with decreasing temperatures as expected from the fact that hypothermic chemical processes can reduce reactions. However, metabolism at a core temperature of 20°C was still at 20% of its normal level. These findings suggest that pig brain activity at this temperature is still high enough to cause diffuse brain damage (i.e., by cell necrosis) if blood circulation is arrested. In addition, it was reported that a neurological sequelae increased in frequency and severity with increasing duration of DHCA, so the time for surgical repair is limited (Bellinger *et al.*, 1995). RCP, also termed antegrade cerebral perfusion or regional low flow cerebral perfusion, was described more than a decade ago as a cerebral support technique for neonatal aortic arch reconstruction (Pigula *et al.*, 1999, 2000). This technique provides antegrade cerebral blood flow by perfusing the brain through a graft sutured to the innominate artery or a small arterial cannula advanced cephalad into the innominate artery. The technique could minimize or eliminate DHCA during aortic arch reconstruction (Asou *et al.*, 1996; Fraser and Andropoulos, 2008; Andropoulos *et al.*, 2013). It was also demonstrated that in addition to providing cerebral oxygenation, RCP provided blood flow to the subdiaphragmatic organs as well (Pigula *et al.*, 2000). In addition, Jiang *et al.* (2006) demonstrated experimentally the superiority of deep hypothermic perfusion in mammals. The advantage of RCP is that it allows a much longer interval of safe circulatory arrest, since the supply of nutrients and oxygen at a relative low flow allows maintenance of appropriate levels of oxygen metabolism at hypothermic temperatures (Griepp, 2001).

Contemporary techniques for RCP have varied significantly. The RCP bypass flow rates in published articles have varied from 20 to 94 mL/(kg·minute) (Andropoulos *et al.*, 2003a, 2003b, Visconti *et al.*, 2006; Goldberg *et al.*, 2007; McQuillen *et al.*, 2007). Monitoring techniques during RCP have varied from none (Goldberg *et al.*, 2007), to arterial pressure only (Visconti *et al.*, 2006), to near infrared spectroscopy (NIRS) for cerebral oxygenation (Pingula *et al.*, 2000), and also, transcranial Doppler ultrasound (TCD) (Andropoulos *et al.*, 2003a, 2003b).

The studies with inadequate RCP flows cannot show the superiority or equivalence of RCP versus DHCA. Goldberg *et al.* (2007) prospectively randomized 77 neonates undergoing Norwood Stage I palliation for HLHS to DHCA or RCP (39 RCP, 38 DHCA). RCP was initiated at 5 mL/(kg·minute), and increased to 20 mL/(kg·minute). Again, cerebral NIRS was used, but no adjustments to RCP flow rates were made on this basis. Both RCP and DHCA times were a mean of 41 minutes, but the RCP group required a mean of 5.7 minutes of DHCA. Because of technical and anatomic considerations, 3 of 39 RCP patients required significant periods of DHCA, but were kept in the RCP group for analysis. Of the 57 survivors at 1 year, 27 were in the RCP group, and 30 in the DHCA group. At 1 year, the Bayley Scales of Infant Development II scores were not different between groups, with the Mental Development Index 94 for DHCA (28 patients) versus 89 for RCP (22 patients), and the Physical Development Index 80 for DHCA versus 74 for RCP.

In this study, the flow rate was kept more than 40 mL/(kg·minute) during RCP, to maintain an adequate cerebral blood flow and oxygen delivery. It was reported that at 30 mL/(kg·minute), 1 of 10 patients had no detectable left MCA blood flow, at 20 mL/(kg·minute), 2 of 10 had no left MCA flow, and at 10 mL/(kg·minute), 3 of 10 had no detectable left MCA flow. Cerebral rSO₂ and jugular venous bulb oxygen saturation declined from baseline at 20 and 10 mL/(kg·minute). Measurements were made after 2 minutes at each flow level, because the investigators did not allow the cerebral saturation to decrease further (Fraser and Andropoulos, 2008). In addition, in our previous study, TCD results showed that at 30 mL/(kg·minute), the MCA blood flow cannot maintain a continuous flow in the main cerebral artery in some cases (Zhang *et al.*, 2009). These data are direct evidence that the RCP flows of 30 mL/(kg·minute) or less, which are frequently used in the studies cited above, are inadequate for a number of patients. Inadequate flow RCP may actually be worse than DHCA, as the RCP times in the studies cited are 40–70 minutes, longer than reported DHCA times.

The animal and human data reviewed above suggest that RCP flows, with the technique described by Pigula *et al.* (2000), should be at least 40 mL/(kg·minute) or more for most patients, again guided by neuromonitoring (Hofer *et al.*, 2005; Amir *et al.*, 2006; Chock *et al.*, 2006; Schears *et al.*, 2006). Flows less than this are consistently associated with the development of low cerebral oxygen tensions, placing the patient at risk, which may be dangerous in the absence of monitoring.

In the present study, the mortality rates, the incidence of low cardiac output, renal dysfunction, and lung issues were similar in both groups. The neurologic abnormality rates were

lower in the RCP group. These findings may have resulted from a higher flow rate during RCP as compared to other studies. A sufficient flow is the basis for cerebral protection during circulatory arrest. In addition, to improve the neurologic protection, pH-stat blood gas management was used in all cases in this study. It was demonstrated that the use of pH-stat strategy in infants undergoing deep hypothermic CPB was associated with a trend toward lower postoperative morbidity and with a significantly shorter recovery time to first EEG activity (du Plessis *et al.*, 1997). Hagl *et al.* (2001) showed that the incidence of temporary neurological dysfunction, which reflects the adequacy of cerebral protection, is clearly lower with RCP than DHCA. It was reported that with the use of RCP, however, the average quality of life score was significantly better in comparison with an age-matched and gender-matched standard population at each time period and allows the extension of DHCA up to 30 minutes (Immer *et al.*, 2004).

Andropoulos *et al.* (2013) reported that lower maternal intelligence, longer intensive care unit length of stay, higher benzodiazepine dose, and longer DHCA times were associated with lower cognitive scores. A longer RCP time was also associated with higher cognitive scores. They concluded that the duration of the RCP was not associated with adverse outcomes. In fact, longer RCP was associated with improved cognitive scores in that study. This suggests that RCP, even when prolonged, is a safe and effective technique for cerebral support during neonatal arch reconstruction, a result that is supported by our study. In addition, the neurodevelopment outcomes for this RCP cohort demonstrate that this technique is effective and safe in supporting the brain during complex congenital cardiac defect repair.

The limitations of this study were first, only the hospital records were reviewed without the long-term follow-up results. In children, the neurodevelopment outcomes such as with attention, fine and gross motor control, visual motor integration, and executive functioning, are very important. Second, no formal psychometric studies were performed. All complications were defined mainly according to the clinical feature. It may cause some bias in the study. Third, the neurologic monitoring was not used in all cases. It was suggested that in the absence of such monitoring, the individual patient was at risk for cerebral hypoperfusion and hypoxemia (Fraser and Andropoulos 2008).

Conclusion

RCP is a promising CPB technique with increasing experimental and clinical data supporting its use. If adequate RCP flows of 40 mL/(kg·minute) or above for most patients are used, the brain should be well protected against hypoxic insults. In summary, RCP, with enough flow rate, is a reliable and safe technique for cerebral protection during circulatory arrest in children and it facilitates complex and time-consuming procedures.

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Disclosure Statement

All authors declare that no competing financial interests exist.

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