Ten years of experience with total perfusion for cerebral and end-organ protection during aortic arch reconstruction in neonates

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Abstract

Introduction. Whole-body perfusion represents a promising alternative to traditional methods, such as deep hypothermic circulatory arrest and antegrade cerebral perfusion, potentially reducing the risks of both neurological complications and acute kidney injury. However, the experience with its application, especially in the most vulnerable group of neonates, remains insufficiently studied and requires systematic analysis of intraoperative and long-term outcomes.

Objective. To evaluate intraoperative and early postoperative outcomes in neonates undergoing aortic arch reconstruction with whole-body perfusion.

Methods. This prospective cohort study evaluated the efficacy and safety of surgical treatment in neonates undergoing aortic arch reconstruction with total perfusion ($n = 43$). The median patient age was 8 (IQR 5–28) days, and median body weight was 3.4 (IQR 2.9–4) kg. Male patients predominated 25 (58.2 %).

Results. The primary endpoint was acute kidney injury assessed using the pediatric KDIGO criteria. Acute kidney injury was observed in 9 (21 %) of patients. The only significant factor for acute kidney injury was the inotropic index on postoperative day 1 (OR = 1.08; 95 % CI (1.01; 1.17)). Neurological complications occurred in 4 (9.3 %) of patients. Hospital mortality was 1 (2.3 %).

Conclusion. Whole-body perfusion represents a straightforward, efficacious, and safe organ protection strategy for neonatal aortic arch reconstruction, demonstrating a low rate of acute kidney injury.

Keywords: aortic coarctation; congenital heart defect; full-flow perfusion; neurological dysfunction; renal dysfunction

Десятилетний опыт применения полнопоточной перфузии для защиты головного мозга и внутренних органов во время реконструктивных операций на дуге аорты у новорожденных

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Аннотация

Актуальность. Полнопоточная перфузия представляет собой перспективную альтернативу таким традиционным методам, как глубокая гипотермическая остановка кровообращения, селективная перфузия головного мозга, поскольку позволяет обеспечить одновременную перфузию головного мозга и нижней половины тела, потенциально снижая риски как неврологических осложнений, так и острого повреждения почек. Однако опыт ее применения, особенно у наиболее уязвимой группы новорожденных, остается недостаточно изученным и требует анализа интраоперационных и отдаленных результатов.

Цель. Оценить интраоперационные и ранние послеоперационные результаты у новорожденных пациентов, перенесших реконструктивные операции на дуге аорты в условиях полнопоточной перфузии.

Методы. В представленном когортном проспективном исследовании выполнена оценка эффективности и безопасности хирургического лечения новорожденных пациентов после реконструктивных операций на дуге аорты с применением полнопоточной перфузии (n = 43). Средний возраст пациентов составил 8 (5; 28) дней, а масса тела – 3,4 (2,9; 4) кг. Мужской пол преобладал в исследовании – 25 (58,2 %).

Результаты. Первичной конечной точкой было острое повреждение почек, оцененное по детской шкале KDIGO. Острое повреждение почек наблюдалось у 9 (21 %) пациентов. Единственным фактором острого повреждения был инотропный индекс в первый день (ОР = 1,08; 95 % ДИ (1,01; 1,17)). Неврологические осложнения наблюдались у 4 (9,3 %) пациентов. Госпитальная летальность составила 1 (2,3 %) случай.

Заключение. Полнопоточная перфузия при пластических операциях на дуге аорты у новорожденных пациентов является простой, эффективной и безопасной методикой органопротекции с небольшой частотой острого повреждения почек.

Ключевые слова: врожденный порок сердца; коарктация аорты; неврологические осложнения; острое повреждение почек; полнопоточная перфузия

Introduction

Successful outcomes in surgical correction involving aortic arch reconstruction in neonates require a "dry" surgical field and adequate neuro- and end-organ protection [1; 2]. For a long time, selective antegrade cerebral perfusion (SACP) was considered the "gold standard" for organoprotection during surgical treatment of congenital aortic arch pathology [3]. SACP reduces the risk of ischemic brain injury by providing continuous cerebral perfusion, but it does not ensure perfusion of the lower body, which increases the risk of acute kidney injury [4]. In 2001, Imoto Y. and co-authors proposed a new perfusion method involving the cannulation of the innominate artery and an additional cannula in the descending aorta to provide whole-body organ perfusion [5]. Although this method has proven effective in many cardiac surgery centers, there is little published information on the efficacy of full-flow perfusion, especially in neonates and infants under one year of age.

The aim of our study was to evaluate intraoperative, as well as early and long-term outcomes in neonatal patients undergoing reconstructive aortic arch surgeries with whole-body perfusion.

Methods

Study Design and Patient Characteristics

The present study performed a prospective analysis of patients in our clinic from June 2018 to January 2024. The study included 43 patients with biventricular correction of congenital obstructive aortic arch pathology (coarctation with hypoplasia of the aortic arch and interrupted aortic arch). The study design is presented in Fig. 1.

Inclusion criteria:
- Biventricular circulation.
- Obstruction at the level of the aortic arch, including aortic coarctation, hypoplasia, or interruption of the aortic arch.
- Surgery performed under cardiopulmonary bypass.
- Age < 1 month.

Exclusion criteria:
- Severe comorbid conditions, including neurological sequelae, infections, acute kidney injury, or necrotizing enterocolitis prior to operation.
- Surgery performed under deep hypothermic circulatory arrest (DHCA).
- Premature with a gestational age < 32 weeks.

Endpoints

Primary Endpoint: Acute kidney injury (AKI), assessed by the pediatric KDIGO scale.

Secondary Endpoints: 30-day mortality and any neurological complications (brain CT or MRI scan was performed in the presence of clinical symptoms), bleeding.

Research methods

In-hospital mortality was defined as a fatal outcome occurring within 30 days from the date of surgery or before hospital discharge, whichever was longer.

Acute kidney injury (AKI) was evaluated using the pediatric KDIGO criteria, based on changes of serum creatinine levels from baseline and urine output over the first three postoperative days [6]. Indications for peritoneal dialysis included: 1) electrolyte abnormalities, such as hyperkalemia refractory to medical treatment; 2) fluid

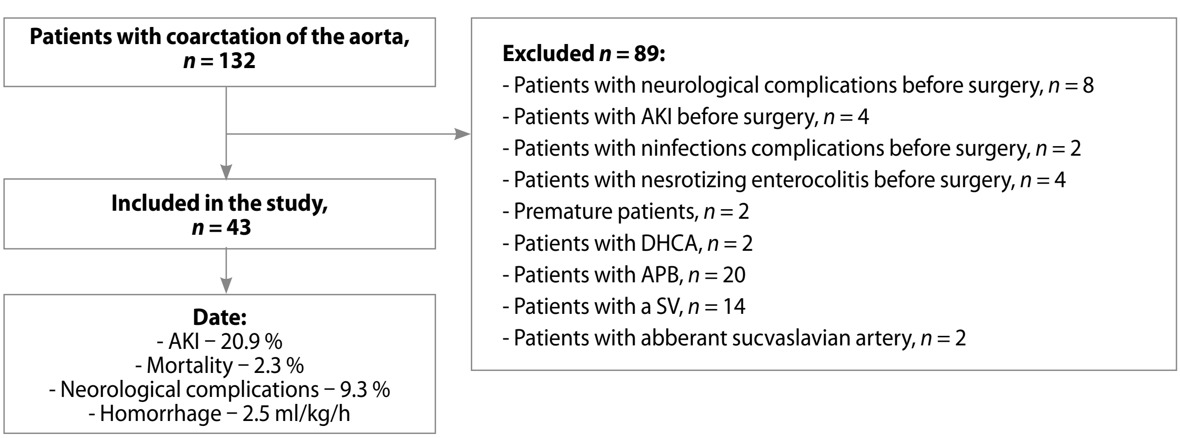

Fig. 1. Study designs

Note. AKI – acute kidney injury; DHCA – deep hypothermic circulatory arrest; IAA – interrupted aortic arch; SACP – selective antegrade cerebral perfusion; SV – single ventricle.

overload; 3) persistent oliguria; 4) persistent metabolic acidosis [7].

Patients were classified as critical if they presented with a closed patent ductus arteriosus (PDA) and signs of organ dysfunction, including anuria and lactate levels above 6 mmol/L upon admission [8].

The dosage of vasoactive drugs was assessed by considering the maximum daily cardiotonic support during the first three postoperative days. The vasoactive inotropic score (VIS) was calculated according to Gaies et al., with modification [9; 10]:

$$\begin{gathered}\text{VIS} = \text{dopamine dose (mcg/kg/min)} + \\ + \text{dobutamine dose (mcg/kg/min)} + \\ 100 \times \text{epinephrine dose (mcg/kg/min)} + \\ + 10 \times \text{milrinone dose (mcg/kg/min)} + \\ + 10{,}000 \times \text{vasopressin dose (units/kg/min)} + \\ + 100 \times \text{norepinephrine dose (mcg/kg/min)} + \\ + 10 \times \text{phenylephrine dose (mcg/kg/min)}.\end{gathered}$$

Neonatal necrotizing enterocolitis (NEC) was assessed based on the modified Bell's criteria [11].

Neurological status was routinely evaluated postoperatively, and in cases where neurological complications were suspected, brain CT or MRI was performed.

Near-infrared spectroscopy (NIRS) (INVOS 5100, Somanetics, USA) was used to assess cerebral and lower body perfusion both intraoperatively and on the first postoperative day. NIRS sensors were placed on the forehead and the back (at the L1–L3 level) to measure tissue oxygen saturation.

Multiorgan failure was defined as the acute dysfunction of two or more organs.

Surgical technique and perfusion methods

The aortic arch reconstruction was performed by four experienced cardiac surgeons using one of the following surgical techniques: 1) "oblique extended" anastomosis [12]; 2) "end-to-side" anastomosis [13]; 3) aortic arch patch repair using pulmonary allograft (Cardiostar LLC, Saint Petersburg, Russia) [14]; 4) "ascending sliding" anastomosis [15]. All patients underwent surgery under the same general anesthesia protocol. A median sternotomy was used in all cases. Blood pressure was monitored via the right radial and femoral arteries. Body temperature was measured using rectal and nasopharyngeal sensors. NIRS was continuously monitored throughout the surgery and 24 hours postoperatively, using forehead and lumbar sensors.

Whole-body perfusion

Two aortic cannulation techniques were used, depending on the anatomy of the ascending aorta. In most cases, the brachiocephalic trunk was directly cannulated through the ascending aorta, with the cannula repositioned to the trunk before aortic reconstruction. In patients with a small ascending aorta, the arterial cannula was inserted through a 4-mm polytetrafluoroethylene (PTFE) vascular graft (Carboflo®/Standard C.R. Bard Inc./IMPRA), which was sutured to the brachiocephalic trunk.

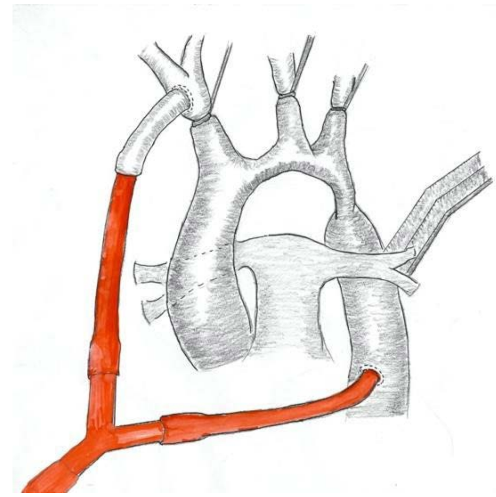

Fig. 2. Whole-body perfusion scheme

When whole-body perfusion (WBP) was performed, a second arterial cannula was inserted into the thoracic descending aorta through the posterior pericardium to ensure perfusion of the lower half of the body (Fig. 2). Cannulas of equal diameter (6–8 Fr) were used to facilitate optimal blood flow distribution. Perfusion in the WBP group was managed using a single pump, with continuous monitoring of the mean blood pressure difference between the radial and femoral arterial lines to prevent hypoperfusion or hyperperfusion. In cases of pressure imbalance between the arterial lines, partial clamping of one arterial cannula was performed to achieve perfusion balance.

CPB was maintained at a perfusion rate of 150 ml/kg, with cooling to a rectal temperature of 30–32 °C in the WBP group and 25–28 °C in the SACP group. In the SACP group, the cooling was performed at least 20 minutes. An α-stat mode was used for blood gases management with measurements every 20 minutes. An antegrade crystalloid cardioplegia (Bretschneider's solution, Custodiol; Dr. Franz Köhler Chemie, Alsbach-Hähnlein, Germany) was administered at a dose of 40 mL/kg into the aortic root.

Statistical Analysis

The Shapiro – Wilk test was used to assess the normality of data distribution. Continuous data are presented as median and interquartile range (25th; 75th percentiles), and categorical data as numbers and percentages.

Table 1. Baseline and demographic characteristics of the patients, $n = 43$

Characteristics	Whole-body perfusion
Height, cm	52 (50; 54)
Weight, kg	3.4 (2.9; 4)
Body surface area, m^2	0.22 (0.20; 0.24)
Sex (male), *n* (%)	25 (58.2)
Age, days	8 (5; 28)
Newborn patients, *n* (%)	40 (93)
Low weight patients, *n* (%)	3 (7)
Patent ductus arteriosus, *n* (%)	31 (72)
Diameter of the patent ductus arteriosus, mm	4.5 (4; 5)
Creatinine before surgery, mmol/l	61 (49; 74)
Critical patients, *n* (%)	7 (16.3)
Septal defects, *n* (%)	33 (76.7)
PaO_2 before surgery, mm.Hg	101 (70; 132)
$PaCO_2$ before surgery, mm.Hg	42 (39; 47)
Saturation right arm, %	92 (87; 97)
Lactate before surgery, mmol/l	1.9 (1.2; 2.6)
Cerebral NIRS before surgery, %	78 (51; 89)
Lumbar NIRS before surgery, %	92 (82; 95)
Interruption of aortic arch, *n* (%)	7 (16.3)
Aortic arch hypoplasia, *n* (%)	36 (83.7)

Note. Presented as the median (25th; 75th percentile) or as numbers (%).

Differences between groups were compared using Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. The result of logistic regression analysis is expressed as an odds ratio with a 95 % confidence interval (95 % CI). A significance level of $p < 0.05$ was adopted. Perfusion protection data analysis was performed using Stata 14 software (StataCorp LP, College Station, USA).

Results

The baseline and demographic characteristics of patients are summarized in Table 1.

As shown in Table 1, the majority of patients were neonates with aortic arch hypoplasia. Most patients had septal defects. The majority of children had patent ductus arteriosus. The median preoperative cerebral oxygenation based on cerebral near-infrared spectroscopy was 78 (51; 89) %.

Intraoperative and early postoperative outcomes are presented in Table 2. There were no intraoperative fatalities.

Table 2. Intraoperative and early postoperative outcomes, $n = 43$

Characteristics	WBP
Minimal temperature, rectal, °C	32.0 (29; 34)
CPB time, min	86 (61; 105)
Aortic cross-clamp time, min	31 (25; 42)
Delayed chest closure, *n* (%)	22 (51)
Inotropic support time, days	5 (3; 6)
Mechanical ventilation time, hours	89 (2; 5)
VIS 24 hours, mcg/kg/min	7 (5; 15)
VIS 48 hours, mcg/kg/min	6 (4.2; 10)
VIS 72 hours, mcg/kg/min	4.5 (1.5; 8)
Creatinine 24 hours, mmol/l	76 (69; 87)
Creatinine 48 hours, mmol/l	72 (64; 87)
Creatinine 72 hours, mmol/l	70 (60; 84)
ICU stay, days	6.5 (5; 8)
Hospital stay, days	21 (18; 25)
Mortality, *n* (%)	1 (2.3)
Acute kidney injury pKDIGO, *n* (%)	9 (21)
pKDIGO 1, *n* (%)	3 (7)
pKDIGO 2, *n* (%)	3 (7)
pKDIGO 3, *n* (%)	3 (7)
Renal replacement therapy, *n* (%)	3 (7)
Neonatal necrotizing enterocolitis, *n* (%)	3 (7)
Sepsis, *n* (%)	1 (2.3)
Intraoperative lumbar NIRS, %	92 (90; 95)
Intraoperative cerebral NIRS, %	90 (83; 93)
PaO_2 after surgery, mm.Hg	200 (166; 208)
$PaCO_2$ after surgery, mm.Hg	36 (30; 41)
Saturation right arm, %	99 (98; 100)
Lactate after surgery, mmol/l	5.2 (4.5; 6.9)
Blood loss in 24 hours, ml/kg	2.5 (12.5; 27.6)
Neurological complications, *n* (%): Subdural hemorrhage, *n* (%) Intraventricular hemorrhage, *n* (%) Subarachnoid hemorrhage, *n* (%)	4 (9.3) 4 (100) 0 (0) 0 (0)

Note. CPB – cardiopulmonary bypass; ICU – intensive care unit; NIRS – near-infrared spectroscopy; VIS – vasoactive inotropic score.

As shown in Table 2, acute kidney injury was present in 9 (21 %) of patients, with 3 (7 %) requiring renal replacement therapy. Neurological complications occurred in 4 (9.3 %) of patients, all of whom had subdural hemorrhage. Mortality was 1 (2.3 %). Sepsis-related complications were

Table 3. Risk factors for acute kidney injury according to KDIGO.

Characteristics	Univariate		Multivariate	
	OR (95 % CI)	*p*	OR (95 % CI)	*p*
Inotropic support time, h	1.1 [1.01; 1.19]	0.021	1.04 [0.98; 1.12]	0.104
VIS 24 hours	1.04 [1.001; 1.12]	0.019	1.08 [1.01; 1.17]	0.025
Minimal temperature, °C	0.86 [0.77; 0.96]	0.011	0.91 [0.67; 1.14]	0.670

Note. VIS – vasoactive inotropic score.

rare in the postoperative period (1 (2.3 %)). Necrotizing enterocolitis developed in 3 (7 %) of children.

Risk factors for acute kidney injury are presented in Table 3.

As shown in Table 3, the only risk factor was the vaso-inotropic index, an increase of which by 1 μg/kg/min increased the risk of acute kidney injury by 8 %.

Discussion

One of the main objectives during aortic arch reconstruction in newborns is to ensure not only a bloodless surgical field but also optimal protection of internal organs [1]. Since 1960, the organoprotective effect during plastic surgeries on the aortic arch has been achieved using Deep Hypothermic Circulatory Arrest (DHCA), as it is a simple and effective strategy. By arresting circulation for a safe period, inversely proportional to body temperature (down to 14.1–20.0 °C), brain metabolism at the cellular level is slowed down, thereby increasing the brain›s tolerance to hypoxia, which provides a neuroprotective effect [16–18]. According to a number of studies by McCullough J.N. and co-authors, a safe period for circulatory arrest at specific temperatures for defect correction has been determined. Thus, the target circulatory arrest time under deep hypothermia (18–20 °C) in the protocols of many cardiac surgery centers is less than 30 minutes [19].

For a long time, DHCA remained the standard method providing organoprotection during surgical repair of aortic coarctation and aortic arch hypoplasia in neonates and infants. However, a number of studies show the development of adverse events in the early postoperative period, including neurological, respiratory, and hematological complications, circulatory disorders, kidney and liver damage due to prolonged cardiopulmonary bypass under deep hypothermia [17; 20]. For example, in the work of Sinelnikov Yu.S. and co-authors, 37.5 % of newborns operated under deep hypothermia during aortic arch reconstruction had neurological complications in the postoperative period [20]. Furthermore, a study by Hughes G.C. and co-authors showed that in the early postoperative period after aortic arch repair, there was a decrease in gray matter, cortical thickness, and impaired connectivity between functional areas, leading to the development of postoperative cognitive dysfunction [16].

To enhance the neuroprotective effect during aortic arch reconstruction, Asou S.O. and colleagues in 1996 proposed a new strategy – selective antegrade cerebral perfusion (SACP), which was also performed under deep hypothermia [1]. However, contradictory results from a number of studies [1; 20–22] led to the performance of SACP under moderate hypothermia (25 °C), which not only reduced the duration of cardiopulmonary bypass but also decreased the incidence of complications in the early postoperative period associated with the effects of low temperatures (capillary leak syndrome, hypocoagulation syndrome, hemolysis) [1]. The reduction in the incidence of neurological complications, compared to DHCA, contributed to SACP becoming the strategy of choice in leading cardiac surgery centers for aortic arch reconstruction in neonates [16]. This is also indicated by the work of Bodrov D.A. and co-authors, where SACP and normothermia were used [23]. However, insufficient collateral blood flow does not provide adequate organoprotection, while an additional factor of visceral organ damage is the effect of low temperatures (32 °C) and reperfusion during rewarming [4; 24].

To prevent the development of neurological complications and visceral organ damage, there was a need to develop a new method for protecting the cerebral and internal organs. Thus, in 2001, Imoto Y. [5] and co-authors proposed whole-body perfusion with dual aortic cannulation (DAC) during aortic arch reconstruction. Thanks to additional cannulation of the descending thoracic aorta through the posterior pericardial leaflet or directly into the lumen of the transected aorta, it simultaneously achieved neuro- and organoprotective effects. From the results of a retrospective study by Hammel J.M. and co-authors, the superiority of whole-body perfusion (with cooling to 32 °C) over SACP in terms of maintaining optimal visceral blood flow is evident [25; 26]. The intraoperative period was characterized by a shorter duration of CPB and aortic occlusion. Given the use of whole-body perfusion with DAC and the reduction in CPB duration, the early postoperative period was associated with better renal filtration and a low incidence of acute kidney injury, which confirms the organoprotective effect [4; 24].

Whole-body perfusion in neonates during aortic arch reconstruction, thanks to additional visceral perfusion, represents a more physiological organ perfusion than SACP. According to a study by Kreuzer M. and co-authors, hospital mortality rates were 2.3 % in the group with simple biventricular anatomy of the defect [27], which is comparable to our previous and current study [24]. In these studies, hospital mortality was not associated with the dual arterial cannulation strategy. In our previous study, the cause of early postoperative mortality was necrotizing enterocolitis, associated with a long duration of infusion and a high dose of prostaglandin E1 in the preoperative period. In this study, the cause of hospital mortality was septic shock. This patient had congenital intrauterine infection detected during intrauterine development, which caused congenital pneumonia. The child underwent emergency surgery, but the early postoperative period was complicated by septic shock.

In the study by Kılıç Y. and co-authors, comparing two perfusion strategies during aortic arch reconstruction in newborns, the advantage of whole-body perfusion over SACP was demonstrated, as the group with whole-body perfusion required peritoneal dialysis less frequently in the early postoperative period than the SACP group [8]. Thus, only 7 % of patients in the whole-body perfusion group required peritoneal dialysis, which is comparable to the data in our study. However, in the study by Tan Recep B.Z. and co-authors, no advantage of whole-body perfusion over SACP was found regarding renal dysfunction, as in this study, lactate, creatinine, and urea levels were higher in the whole-body perfusion than in the SACP group ($p < 0.05$) [28].

Lactate levels were determined as an indicator of organ damage. According to the study by Kreuzer M. and co-authors, the standard lactate value was less than 2 mmol/L [27]. However, in our study, blood lactate levels exceeded those after aortic arch reconstruction and amounted to 5.2 (4.5; 6.9) mmol/L. The study by Fernández-Doblas J. and co-authors demonstrated comparable lactate levels, which tended to decrease after 72 hours [29]. We can hypothesize that elevated lactate levels may be directly related to critical coarctation, as well as prolonged cardiopulmonary bypass during radical correction.

Whole-body perfusion, in addition to protecting internal organs, should also provide a neuroprotective effect [30]. To evaluate the neuroprotective effect after aortic arch reconstruction, we not only assessed clinical data (seizures, limb paresis) but also performed brain MRI on days 5–7 after surgery, as it is possible to visualize asymptomatic lesions [31]. However, according to a number of studies, hemorrhagic foci are more often detected after whole-body perfusion. The results of many studies have shown [1; 24] that the main causes of neurological complications include the use of the a-stat strategy, prolonged cerebral perfusion, and high partial oxygen pressure during patient rewarming. However, we believe that one of the risk factors for neurological dysfunction is low temperatures during perfusion. Compared to our previous study, the development of neurological complications has now decreased due to increased temperature during perfusion.

Also, in the early postoperative period, despite providing visceral perfusion during aortic arch plasty, we observed the development of enterocolitis in 3 (7 %) of newborns, the cause of which was prolonged prostaglandin infusion, with a dose of 5–10 ng/kg/min and a duration of more than 14 days, to prevent the closure of the patent ductus arteriosus and maintain the hemodynamics of newborns in the preoperative period.

Study limitations

A small cohort of patients is one of the limiting factors of our study. We did not perform CT or MRI before reconstructive operations on the aortic arch, which could lead to false-positive results for neurological complications in the postoperative period. In addition, some patients were excluded: patients with univentricular hemodynamics and premature patients as they are more predisposed to the development of acute kidney injury.

Conclusion

Dual arterial cannulation during reconstructive operations on the aortic arch in neonates is an effective and safe method of organ protection, with a low incidence of acute kidney injury and neurological complications.

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