Original Article

Renal Function and Inflammatory Response in Neonates Undergoing Cardiac Surgery With or Without Antegrade Cerebral Perfusion—A Post hoc Analysis

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ABSTRACT

Background: Cardiopulmonary bypass (CPB) may lead to tissue hypoxia, inflammatory response, and risk for acute kidney injury (AKI). We evaluated the prevalence of AKI and inflammatory response in neonates undergoing heart surgery requiring CPB with or without antegrade cerebral perfusion (ACP).

Methods: Forty neonates were enrolled. The patients were divided into two groups depending on the use of ACP. AKI was classified based on the Kidney Disease: Improving Global Outcomes (KDIGO) criteria. Inflammatory response was measured using plasma concentrations of interleukins 6 (IL-6) and 10 (IL-10), white blood cell count (WBC), and C-reactive protein (CRP).

Results: Eight patients (20%) experienced AKI: five (29%) in the ACP group and three (13%) in the non-ACP group ($P = 0.25$). Postoperative peak plasma creatinine and urine neutrophil gelatinase-associated lipocalin were significantly higher in the ACP group than in the non-ACP group [46.0 (35.0–60.5) vs 37.5 (33.0-42.5), $P = 0.044$ and 118.0 (55.4–223.7) vs 29.8 (8.1–109.2), $P = 0.02$, respectively]. Four patients in the ACP group and one in the non-ACP group required peritoneal dialysis ($P = 0.003$). Postoperative plasma IL-6, IL-10, and CRP increased significantly in both groups. There were no significant differences between the ACP and non-ACP groups in any of the inflammatory parameters measured.

Conclusions: No significant difference in the AKI occurrence or inflammatory response related to CPB modality could be found. In our study population, inflammation was not the key factor leading to AKI. Due to the limited number of patients, these findings should be interpreted with caution.

Keywords: Antegrade cerebral perfusion, cardiopulmonary bypass, infant, kidney injury

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INTRODUCTION

Despite recent advances in surgical techniques and treatment modalities, infant cardiac surgery requiring cardiopulmonary bypass (CPB) remains a high-risk procedure with relatively high morbidity and mortality rates.[1] Acute kidney injury (AKI) is one of the complications of CPB with an occurrence rate of around 20–65% in pediatric population.[2-6] AKI has been associated with increased postoperative mortality in children undergoing cardiac surgery,[7] and fluid overload, hypotension and hypoxia, activation of the sympathetic nervous system and renin-aldosterone system, hemolysis, and CPB-associated systemic inflammation have been recognized as risk factors

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for AKI.[2,8-10] The impact of CPB modality on AKI risk has been under discussion. There are only few reports available on CPB and AKI in neonates and the published patient series are understandably relatively small.[11-14]

We have recently conducted a prospective, randomized, double-blinded, placebo-controlled study evaluating the effect of peri- and postoperative stress-dose corticosteroid (SDC) treatment on inflammatory reaction, postoperative ventricle function, and AKI risk in neonates undergoing open-heart surgery.[9,15] We performed a *post-hoc* analysis of this data by dividing the study population into two groups based on whether antegrade cerebral perfusion (ACP) was used or not (non-ACP). There is a significant difference between these two forms of perfusion technique since during ACP, there is only blood flow to the brain and right upper limb. Therefore, during ACP, the visceral organs may be exposed to reperfusion inflammation and hypoxic damage.

We aimed to compare (1) the occurrence of AKI, (2) changes in key AKI biomarkers, such as plasma creatinine (P-Cr), cystatin c (P-Cyc C), and neutrophil gelatinase-associated lipocalin (P-NGAL), urine NGAL (U-NGAL) and Kidney injury molecule-1 (U-KIM-1), and (3) post-CPB inflammatory response between the ACP and non-ACP groups by measuring plasma interleukin-6 (IL-6) and -10 (IL-10), C-reactive protein (P-CRP), and white blood cell count (B-WBC). Based on our previous findings, we hypothesized that reperfusion-induced inflammation is not the major cause of AKI in ACP-treated infants.

METHODS

The study was approved by the Ethics Committee of Helsinki University Hospital and by the Finnish Medicines Agency. This study was part of the clinical outcome trial registered in the European Union Drug Regulating Authorities Clinical Trials database (Eudra-CT 2011-005239-14). The study design and outcomes related to inflammation, adrenal insufficiency, hemodynamic outcome, and renal function have been published recently.[9,15] Written informed consent was obtained from all parents of the patients before the study commenced.

A total of 51 neonates were eligible for the study; however, 11 patients were excluded due to parental refusal. Forty neonates (age ≤28 days) who were undergoing elective open-heart surgery with CPB due to congenital heart defects between April 2012 and October 2014 were finally enrolled. The decision about using antegrade cerebral perfusion (ACP) was made case by case depending on clinical factors. Antegrade cerebral perfusion (ACP) was used in patients who underwent isolated aortic arch reconstruction or arch reconstruction with another procedure [Table 1]. In the non-ACP group, standard aortic and bicaval cannulation techniques were used. Balanced anesthesia was attained with sufentanil, pancuronium, propofol or (S)-ketamine, and sevoflurane. CPB was established by using a pediatric hollow-fiber membrane oxygenator with a cardiotomy reservoir and a roller pump. Blood flow velocity and target body temperature were prescribed depending on the CPB modality and type of operation. In the ACP group, the blood flow was 15–30 mL/kg/min during ACP and target body temperature was 24°C–28°C while in the non-ACP group, the respective values were 150 mL/kg/min and 32°C–34°C. The pump prime solution consisted of packed red cells, fresh frozen plasma, and albumin. The hematocrit was adjusted to 30%. During rewarming, it increased to between 35 and 45% by hemofiltration and by adding packed red cells as necessary. The acid-base status was managed by using the modified alpha-stat protocol. Fresh gas flow in the CPB circuit was decreased in hypothermic patients in order to keep the arterial carbon dioxide tension ($PaCO_2$) values determined at a temperature of 37°C in the upper normal levels or higher. Near-infrared spectroscopy NIRO-100 (Hamamatsu Photonics, Hamamatsu, Japan) was also used to detect a possible decrease in brain oxygenation at low $PaCO_2$ values.

In the ACP group, continuous low-flow cerebral perfusion was maintained by advancing an aortic cannula from the distal ascending aorta into the innominate artery or via a Gore-Tex graft sewn to the innominate artery. Bilateral cannulation was not performed due to a significant risk for thromboembolic events and

Table 1: Type of heart defect and type of surgery performed in the neonates undergoing cardiac surgery with or without antegrade cerebral perfusion

	ACP *n*=17	Non-ACP *n*=23
Surgery, *n* (%)		
HLHS/UVH, Norwood-type repair	7 (41.2)	
HAA+Coa, Aortic arch reconstruction	8 (47.0)	
TGA+HAA, ASO+Aortic arch reconstruction	2 (11.8)	
TGA, ASO		16 (69.6)
VSD+Coa repair end-to-end		1 (4.3)
Truncus arteriosus repair		1 (4.3)
TOF repair		1 (4.3)
TAPVD repair		3 (13.0)
VSD+ASD repair		1 (4.3)

HLHS, Hypoplastic left heart syndrome; UVH, Univentricular heart; HAA, Hypoplastic aortic arch; Coa, Coarctation; TGA, Transposition of great arteries; ASO, Arterial switch operation; VSD, Ventricle septum defect; TOF, Tetralogy of Fallot; TAPVD, Total anomalous pulmonary venous drainage; ASD, Atrium septum defect

disturbances in brain circulation. Cerebral near infrared spectroscopy (NIRO-200NX, Hamamatsu Photonics K. K.) was recorded during the whole procedure to ensure adequate cerebral perfusion. Myocardial protection was accomplished by using a two-minute infusion of cold (24°C) blood cardioplegia, mixed at a ratio of 1:1 (blood:cardioplegia) during aortic cross clamp; after that, a one-minute infusion of cold blood cardioplegia was administered every 20 minutes. According to the original study protocol, half of the patients were randomized to receive an intravenous bolus of methylprednisolone (MP) 2 mg/kg, followed by hydrocortisone infusion 0.2 mg/kg/h six hours after the surgery with a tapering dose during a maximum of five days' stay in the pediatric intensive care unit (PICU). The other half received a saline bolus at the induction of anesthesia and a placebo infusion in a similar fashion as the treatment group. All patients were operated by three experienced surgeons and a perfusion team. Milrinone or/and levosimendan were used as the first-line inotropes, and epinephrine or/and norepinephrine was added to support hemodynamics when needed.

Definition of AKI was based on the Kidney Disease: Improving Global Outcomes (KDIGO) classification as at least 50% or ≥26.5 μmol/L increase in P-Cr concentration from the lowest value, urine output less than 0.5 mL/kg/h lasting at least 6 h, or need for acute dialysis after the operation.[16] Dialysis was initiated due to decreased urine output, hypervolemia, and/or elevated plasma creatinine (P-Cr).

Sample acquisition

Blood samples were obtained at anesthesia induction before the study drug or saline bolus was administered (T1), five minutes after weaning from CPB (T2), six hours after weaning from CPB (T3), and thereafter at 6 a. m. on the following five postoperative days (T4-8). Urine samples were collected at time points T1 and T3-6. The collected blood and urine samples were processed and stored at -70°C for later analysis. P-Cr and P-Cys C concentrations were analyzed in the Helsinki University Hospital laboratory (HusLab, Helsinki, Finland) using standard procedures. P-NGAL and urine (U-NGAL) concentrations of NGAL and urine concentration of KIM-1 and creatinine (U-Cr) were analyzed using commercial ELISA kits (Quontikine, R&D Systems, UK). All samples were analyzed in duplicate. U-NGAL and -KIM-1 results were divided by the corresponding urinary creatinine concentration to standardize the changes in urine concentration. Urine NGAL and KIM-1 samples were lacking from six patients (ACP n = 3, non-ACP n = 3) due to inadequate sample collection. Physiological and clinical outcome parameters, such as urine output and need for vasoactive infusions, were also recorded. Information regarding peritoneal dialysis was collected from the intensive care database (Centricity Critical Care Clinisoft, GE Healthcare, Helsinki, Finland).

The inflammatory response was evaluated by measuring plasma concentrations of interleukins 6 (IL-6) and 10 (IL-10), plasma C-reactive protein (CRP), and white blood cell count (WBC). The plasma IL-6, and IL-10 concentrations were determined using commercial ELISA kits (Quantikine, R&D Systems, Abington, UK) as described earlier.[9]

Statistics

This was a *post-hoc* analysis. Numerical data are presented as mean (SD; range) or median (interquartile range) as appropriate. Wilcoxon rank sum test or Chi-squared comparison or Fisher's exact test was used for categorical data to compare groups with respect to background characteristics. Repeated measurements were compared using the Friedman Test to answer the research question of whether there were changes in the parameters across time points within the two study groups. Mann-Whitney test was performed between different groups at different time points. *P* values less than 0.05 were considered to be statistically significant.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS/Windows version 19.0, SPSS Inc., Chicago, IL, USA).

RESULTS

Subjects and demographics

There were no significant differences in the baseline demographics between the ACP (n = 17) and the non-ACP (n = 23) group as shown in Table 2. Preoperative P-Cr and P-Cys C tended to be higher among the ACP patients; however, the difference did not reach statistical significance [Table 2]. None of the patients required dialysis prior to surgery. The underlying diagnosis differed between the groups. Norwood procedure dominated in the ACP (41.2%) group while in the non-ACP group, the majority of the operations were corrections of transposition of great arteries (69.6%). Due to the unequal distribution of diagnoses between the groups, the RACH score was significantly higher for patients in the ACP group than in the non-ACP group [Table 2].

Postoperative outcome

The 30-day mortality rate was 5.0% [Table 3]. One patient died after truncus arteriosus repair, followed by ECMO treatment, while another tetralogy of Fallot patient with

Table 2: Patient demographics and perioperative data in the neonates undergoing cardiac surgery with or without antegrade cerebral perfusion

Variable	ACP *n*=17	Non-ACP *n*=23	*P*
Age, days	7.0±2.4	8.0±4.2	0.140
Weight, kg	3.4±0.5	3.5±0.5	0.602
Male gender, *n* (%)	9 (53.0)	18 (78.0)	0.177
Gestational age, weeks	39.2±1.5	39.8±1.2	0.722
Ventilation support before operation, *n* (%)			
No support	15 (88.0)	16 (70.0)	0.256
Nasal CPAP	1 (6.0)	4 (17.0)	0.632
Mechanical ventilation	1 (6.0)	3 (13.0)	0.624
RACHS score	4 (4-6)	3 (3-3)	<0.001
Baseline P-TnT, ng/L	50.0 (33.5-72.8)	43.0 (30.0-75.0)	0.558
Baseline P-Cr, μmol/L	42.0±10.54	36.5±4.50	0.188
Baseline P-Cys C, mg/L	1.58±0.28	1.36±0.34	0.056
SDC, *n* (%)	9 (53.0)	11 (49.0)	1.000
CPB support time, min	179.0±46.0	165.0±60.0	0.452
ACC time, min	89.6±35.4	100.4±41.3	0.402
ACP time, min	50±13.4		

CPAP, Continuous positive airway pressure; RACHS, Risk adjustment in congenital heart surgery; P-TnT, Plasma Troponin T; P-Cr, plasma creatinine, P-Cys C; plasma cystatin C; SDC, stress-dose corticosteroid; CPB, Cardiopulmonary bypass; ACC, Aortic cross clamp; ACP, Antegrade cerebral perfusion. Values are mean±standard deviation (SD) or number of patients (%)

Table 3: Patient demographics and perioperative data in the neonates undergoing cardiac surgery with or without antegrade cerebral perfusion

Variable	ACP *n*=17	Non-ACP *n*=23	*P*
pH on arrival to PICU	7.401±0.0891	7.427±0.0895	0.370
P-Lactate on arrival to PICU, mmol/L	4.894±2.183	3.761±1.534	0.061
$ScvO_2$ on arrival to PICU, %	55.8±13.2	62.1±14.8	0.094
PICU days	10.0 (6.5-12.0)	7.0 (5.0-9.0)	0.046
Intubation days	6.9 (4.0-10.0)	4.1 (3.2-5.9)	0.087
First inotrope score at PICU	27.4±8.6	22.4±6.8	0.048
Inotrope score 24 h	18.1 (14.0-28.5)	13.9 (10.6-24.3)	0.133
Inotrope score 48 h	12.5 (9.8-25.8)	12.1 (7.5-21.6)	0.600
Hospital mortality, *n* (%)	0 (0)	2 (8.7)	0.499
AKI, *n* (%)	5 (29.4)	3 (13.0)	0.250
Dialysis, *n* (%)	4 (23.5)	1 (4.3)	0.003
Diuresis POD1, mL/kg	73.1±24.6	76.0±22.6	0.253
Balance POD 1, mL	21.0 (-10.5-82.5)	13.0 (-11.0-40.0)	0.366
P-ProBNP at T_3, ng/L	17 440±844	19 165±9610	0.602
Peak P-Cr, μmol/L	46.0 (35.0-60.5)	37.5 (33.0-42.5)	0.044
Peak P-Cyc C, mg/L	1.50±0.30	1.48±0.19	0.812
Peak P-NGAL, ng/mL	29.5 (22.4-35.8)	33.9 (22.2-43.6)	0.536
Peak U-NGAL/Cr, ng/mg	118 (55.4-223.7)	29.8 (8.1-109.2)	0.020
Peak U-KIM-1/Cr, ng/mg	25.3 (10.3-36.3)	21.0 (6.6-35.1)	0.637
Peak B-WBC, E9/L	10.4 (9.1-13.1)	9.6 (8.0-10.5)	0.089
Peak P-CRP, mg/L	75.8±40.2	109.5±63.7	0.079
Peak P-IL-10, pg/mL	206.7 (65.5-329.3)	192 (44.6-426.1)	0.978
Peak P-IL-6, pg/mL	201.0 (150.7-771.8)	371.1 (173.4-981.9)	0.678

ACP, Antegrade cerebral perfusion; P, Plasma; PICU, Paediatric intensive care unit; $ScvO_2$, Central venous saturation; AKI, Acute kidney injury; POD, Postoperative day; ProBNP, N-terminal pro b-type natriuretic peptide; T_3, six hours after cardiopulmonary bypass; P-Cr, plasma creatinine, P-Cys C; plasma cystatin C; NGAL, Neutrophil gelatinase-associated lipocalin; U, Urine; KIM-1, Kidney injury Molecule-1; B, Blood; WBC, White blood cell count; CRP, C-reactive protein; IL, Interleukin Values are presented as mean±standard deviation if normally distributed, as median and interquartile range in parenthesis if not normally distributed, or as number of patients (%)

severely hypoplastic pulmonary arteries died of multiple organ failure. The median length of stay in PICU was 7.5 (5–10) days, being longer in the ACP group than in the non-ACP group [Table 3]. On arrival to PICU, the ACP group had a significantly higher inotropic score than the non-ACP group; however, after POD 1, no significant difference could be found [Table 3]. Arterial postoperative lactate was also higher until POD 3 in the ACP group than in the non-ACP group [Figure 1].

Renal function

A total of eight patients (20%) experienced AKI; five (29%) in the ACP group and three (13%) in the non-ACP group. Peritoneal dialysis was started in four patients in the ACP group and in one patient in the non-ACP group ($P = 0.003$) [Table 3]. In both groups, all measured renal parameters increased significantly after the operation, except for P-Cr concentration and U-NGAL/Cr ratio in the non-ACP group [Figure 1]. Postoperative P-Cr was

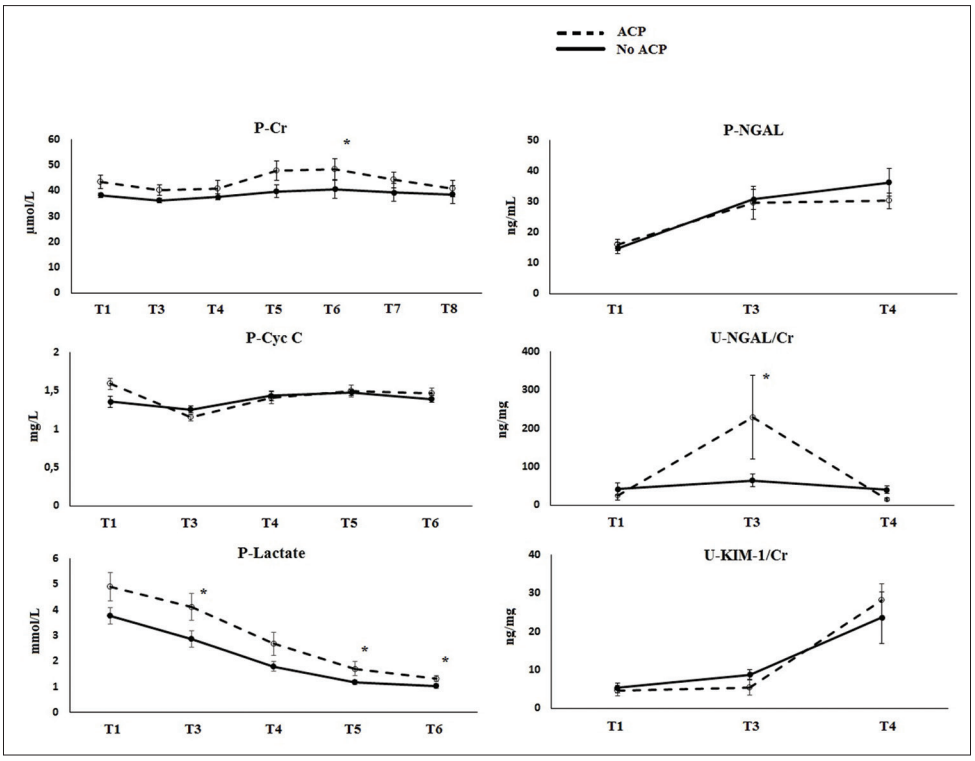

Figure 1: The mean plasma creatinine, cystatin C, lactate, neutrophil gelatinase-associated lipocalin, urine NGAL/creatinine ratio and Kidney injury molecule-1/creatinine ratio preoperatively, at 0 and 6 hours after cardiopulmonary bypass, and on postoperative days 1 to 6. (ACP, dotted line and non-ACP solid line; *, ***P***<0.05)

significantly higher on POD3 in the ACP group than in the non-ACP group [Table 3 and Figure 1] and U-NGAL/Cr ratio was higher six hours after CPB, respectively [Figure 1]. There were no statistically significant differences between the groups in P-Cyc C, P-NGAL, or U-KIM-1/Cr ratio [Figure 1 and Table 3].

Inflammatory response in ACP and non-ACP groups

IL-6, IL-10, and CRP increased significantly after the operation in both groups [Figure 2] while WBC remained relatively unchanged. There were no significant differences between the ACP and non-ACP group in any of the inflammatory parameters measured [Table 3 and Figure 2]. Perioperative MP was given to equal proportions of patients in both groups [Table 2].

DISCUSSION

The overall prognosis of infants undergoing open cardiac surgery requiring cardiopulmonary bypass (CPB) has improved significantly in recent decades. However, despite this progress, open-heart surgery remains a high-risk procedure with relatively high morbidity and mortality rates.[1] In many cases, the general condition of an infant with a congenital heart defect is unstable, which further increases these risks. AKI is one of the complications of CPB and it has been shown to increase mortality in neonates.[2-6] One possible explanation for CPB-induced AKI is inflammatory response, induced by foreign surfaces in the perfusion set, surgical trauma, anesthesia, and insufficient organ perfusion due to CPB. In the present study, we compared the prevalence of AKI in infants with or without ACP and the inflammatory response in these groups. In our study population, the occurrence of AKI was relatively low, being only 20%. We did not find any significant difference in either AKI prevalence or level of inflammation between the two groups. However, patients treated with ACP had significantly higher postoperative peak P-Cr and they required more often peritoneal dialysis, suggesting that AKIs were more severe in the ACP group than in the non-ACP group.

The slightly higher P-Cr and U-NGAL/cr ratio found in ACP-treated patients was not associated with inflammatory response. We could not find significant differences in the levels of IL-6, IL-10, CRP or WBC between the two groups. Cardiac surgery and CPB induce systemic inflammatory response leading to increased concentrations of circulating cytokines.[17,18] This inflammatory response has been linked to an increased risk for organ damage and multiorgan failure. Our previous data in this same patient material suggested that perioperative MP does not influence AKI occurrence, suggesting that CPB-related inflammatory response is not the major cause of AKI.[15]

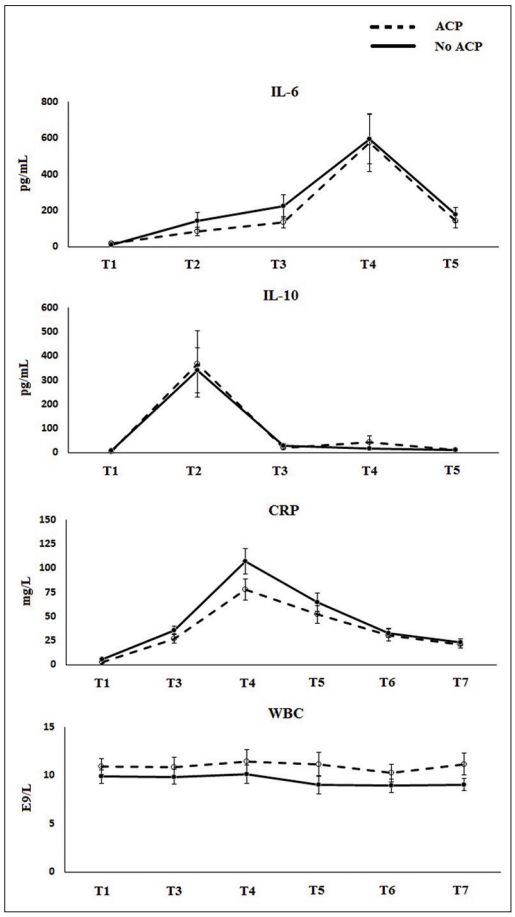

Figure 2: The plasma interleukin 6 and 10, C-reactive protein and white blood cell count measured preoperatively, at 0 and 6 hours after cardiopulmonary bypass (CPB), and on postoperative days 1 to 5. (ACP, dotted line, and non-ACP solid line)

Regional perfusion modality has been developed to prevent neurological morbidity in children undergoing cardiac surgery.[19,20] However, there has been increasing concern about the effect of ACP on other organ systems, such as the liver, kidneys and intestine.[13,14] Therefore, alternative perfusion methods have been developed.[13,21] Recently, double perfusion methods have been introduced in order to avoid both cerebral and visceral hypoperfusion and the risk for end-organ damage.[13,22] The study by Fernández-Doblas *et al*. compared double-perfusion technique and ACP in neonates undergoing aortic arch repair.[13] In this non-controlled study, patients with double-perfusion had significantly higher urine output intraoperatively, but no significant difference in plasma creatinine or estimated GFR. However, the authors were able to show better liver function in patients treated with double-arterial cannulation. This finding is supported by the retrospective study of Kreuzer *et al*. describing outcome in 407 children. ACP may pose a significant risk for visceral hypoperfusion leading to kidney and liver failure.[23] The use of double-artery cannulation has also been introduced at our center in the treatment of high-risk patients. The second cannula is typically inserted into the descending aorta. The major risk in this technique is bleeding during decannulation, which may further lead to arrhythmias and hemodynamic disturbances.

The present study has several shortcomings. First, the number of patients was small and due to various reasons, urine samples were not available from all patients. However, all samples were collected prospectively and the patients were meticulously documented and followed up. Second, as in most previous studies, there were differences in the severity of the underlying heart defect between the ACP and non-ACP groups, which may have influence on postoperative AKI risk. Third, this was a post-hoc analysis of our double-blinded, placebo-controlled study designed to compare anti-inflammatory response, adrenocortical function, and hemodynamic outcome of stress-dose corticosteroid and placebo groups, and the present study was therefore not powered to show differences in kidney injury biomarkers or the incidence of AKI in ACP versus non-ACP groups. Fourthly, the creatinine-based AKI criterion is relatively insensitive among neonates, which may have led to underdiagnosis of AKI in this study.

In conclusion, the AKI occurrence was 29.4% in the ACP group and 13.0% in the non-ACP group. The difference did not reach statistical significance. However, patients in the ACP group appeared to have more severe AKI, since dialysis was required significantly more often in the ACP-treated patients. Our observations about inflammatory biomarkers suggest that CPB-related inflammatory response is probably not the major factor leading to AKI in these patients. Because the present study was not powered to show differences in kidney injury biomarkers or the incidence of AKI, but rather in the inflammatory response, these findings should be interpreted with caution, and future studies with larger study populations are needed.

Clinical trial registry number Eudra-CT 2011-005239-14.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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