Incidence and outcome of acute kidney injury after open heart surgery in children

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Introduction. Cardiac surgery with cardiopulmonary bypass (CPB) is commonly perceived as a risk factor for decline in renal function. Hypothermia, hypoxia, hypotension, non-pulsatile blood flow during CPB, use of ACE inhibitors, inotropic and (or) vasoactive support affect kidney and contribute to the acute kidney injury (AKI).

Objective. To evaluate incidence and outcome of AKI in children undergoing open heart surgery.

Methods. We conducted a prospective, non-randomized observational study at the tertiary care of the University Children's Hospital Pediatric ICU. We enrolled 30 patients, 12 boys and 18 girls with CHD. Their median body weight was 6.8 kg (IQR 5.2 < 8.2 kg) and the median age was 7 months (IQR 5 < 10 months). SCr was determined and preoperative and postoperative creatinine clearance (ClCr) was estimated using the Schwarz formula. During surgical repair and till the end of the first 24 hours urine was collected to measure ClCr, using the difference in urine (UCr) and SCr concentrations. Urine output, body temperature, duration of aortic cross clamping and cardiopulmonary bypass were recorded.

Results. Median intraoperative urine output was 2.4 ml/kg/h (IQR 1.29 < 3.15 ml/kg/h). Median CPB time was 147 min, IQR 116.75 < 205 min, median aortic cross-clamping time was 95 min, IQR 70.5 < 133 min, cooling during CPB to 29.75 °C. Intraoperative SCr rised to 35 μmol/l (IQR 27.5 < 50.5) vs. preoperative SCr 29 μmol/l (IQR 24 < 32.9), $P < 0.0001$. GFR declined from preoperative 98.4 ml/min/1.73 m^2 (IQR 89.6 < 123.04) to intraoperative 39.8 ml/min/1.73 m^2 (IQR 24.9 < 65.5), $P < 0.0001$. Observed incidence of AKI was 30% (9/30). We observed statistically significant ($P = 0.006$) inverse correlation ($r = 0.522$) between CPB time and ClCr.

Conclusions. Open heart surgery in children has severe, but transient effect on expression of renal biomarkers. Observed incidence of AKI was 30% (9 from 30 of our patients). Before discharge from the hospital both biomarkers returned to normal values.

Key words: acute kidney injury, renal biomarkers, creatinine clearance, pediatric open heart surgery

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INTRODUCTION

Cardiac surgery with cardiopulmonary bypass (CPB) is commonly perceived as a risk factor for decline in renal function. Acute kidney injury (AKI), depending on the specific definition, occurs in up to 52% of all patients who undergo open heart surgery (1–15). AKI that requires renal replacement therapy (RRT) occurs in approximately 1% (1, 2, 4). The development of kidney injury is associated with a high mortality, a more complicated hospital course, and a higher risk for infectious complications (2). AKI has a notable increased morbidity risk, including longer duration of ventilation and overall length of stay (12). Even minimal changes in serum creatinine that occur in the postoperative period are associated with a substantial decrease in survival (10). Furthermore, the majority of patients, who develop AKI that requires dialysis, remain dialysis dependent, leading to significant long-term morbidity and mortality (13). Pediatric patients comprise an ideal and informative population for the study of AKI biomarkers as they do not exhibit common adult comorbidities that complicate similar studies in adults, such as diabetes, hypertension, atherosclerosis, and nephrotoxin use (15). All subjects started with normal kidney function, and the study design allowed for the precise temporal definition of altered expression of biomarkers.

OBJECTIVE

Our goal was to evaluate incidence and outcome of AKI in children undergoing open heart surgery. As an indicator of AKI, we used perioperative changes in serum creatinine (SCr) and creatinine clearance (CrCl). pRIFLE classification was used to assess AKI.

METHODS

We conducted a prospective, nonrandomized observational study at the tertiary care University Children's Hospital, 12-bed surgical ICU during 2010–2011 years. The study protocol was approved by the Hospital Ethics Commission. Inclusion criteria were as follows: body weight less than 10 kg (1) and intact renal functions (2). We enrolled 30 patients, 12 boys and 18 girls with CHD (Table 2). Their median body weight was 6.8 kg (IQR 5.2 < 8.2 kg) and the median age was 7 months (Table 1). There were 15 (50%) patients with ventricular septal defect (VSD), 7 (23.4%) patients had atrioventricular septal defect (AVSD), one (3.3%) had total anomalous pulmonary venous drainage (TAPVD), 3 (10%) had Tetrology of Fallot (TOF), 3 (10%) had transposition of great arteries (TGA), and one (3.3%) had AVSD with tricuspid stenosis (Table 2). The SCr level was determined by the Jaffé's method (Cobas 6 000 analyzer, Roche) and preoperative and postoperative ClCr without urine collection was estimated using the Schwarz formula (16): CrCl in ml/min/1.73 m² = k × L/SCr, where k is the proportionality constant (0.33–0.45, depending on maturity) and L is the length in centimeters. During the surgical repair and till the end of the first 24 hours after surgery urine was collected to measure ClCr, using the difference in urine (UCr) and SCr concentrations, using the standard formula: CrCl in ml/min/1.73 m² = (UCr × urine output

Table 1. Demographic data

Variable	Median	IQR	Range
Age, months	7.5	5 < 10	0.3 < 26
Body weight, kg	6.4	5.2 < 8.2	2.88 < 10

Table 2. Characteristics of patients

Heart lesion	No. of pts	%
AVSD (Atrioventricular septal defect)	7	23.4
ASD (Tricuspid stenosis)	1	3.3
VSD (Ventricular septal defect)	15	50.0
TAPVD (Total anomalous pulmonary vein drainage)	1	3.3
TGA (Transposition of great arteries)	3	10.0
TOF (Tetralogy of Fallot)	3	10.0
Total:	30	100.0

(ml)) / (SCr × time in hours × 60) × (1.73/BSA), where UCr is urinary creatinine, SCr is serum creatinine and BSA is the body surface area. Urine output, the lowest body temperature during CPB, aortic cross clamping and cardiopulmonary bypass time were recorded.

Statistical methods

Statistics was performed with the help of the statistical software package MS Excell Data Analysis tool. Continuous variables were presented as median and interquartile range (IQR). Dispersion analysis using one-way analysis of the variance test was used to determine the difference between SCr and ClCr values at different time points: before the surgery (1), on the following morning, <12 hours after completion of the surgery (2) and before discharge of the patient from hospital (3). Pearson's correlation was used to find a correlation between CPB and ClCr.

RESULTS

Median CPB time was 147 min, IQR 116.75 < 205 min, median aortic cross-clamping time was 95 min, IQR 70.5 < 133 min, cooling during CPB to 29.75 °C. Median perioperative (from the start of surgery till the following morning <24 hours) urine output was 2.4 ml/kg/h (IQR 1.29 < 3.15 ml/kg/h) (Table 3). Postoperative median SCr raised to 35 μmol/l (IQR 27.5 < 50.5) versus preoperative median SCr 29 μmol/l (IQR 24 < 32.9), $P < 0.0001$. Median ClCr declined from preoperative 98.4 ml/min/1.73 m^2 (IQR 89.6 < 123.04) versus postoperative 39.8 ml/min/1.73 m^2 (IQR 24.9 < 65.5), $P < 0.0001$ (Table 4, Figs. 1, 2). We find statistically significant ($P = 0.006$) inverse correlation (r = 0,522) between CPB time and ClCr (Fig. 3). According to pRIFLE criteria (50% decrease in ClCr), we detected in 30% (9/30) of our patients compliance with AKI (Fig. 4).

Table 3. CPB variables

Variable	Median	IQR	Range
CPB time, min	147	116.75 < 205	50 < 286
Aortic cross-clamping time, min	95	70.5 < 133	25 < 185
Lowest body temperature, °C	29.75	27.48 < 30.83	19 < 32
Urine output, ml/kg/h	2.41	1.29 < 3.15	0.47 < 7.76

Table 4. Perioperative changes in SCr and CrCl

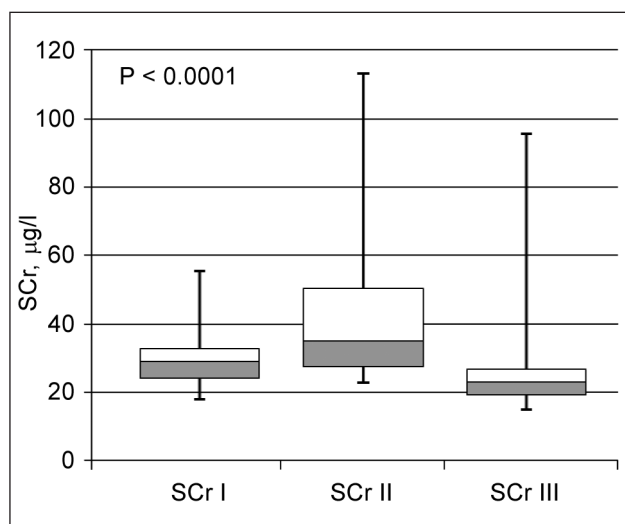| Variable	Before surgery	After CPB	Before discharge
SCr, μmol/l	29 (24 < 32.9)	35 (27.5 < 50.5)	23 (19.3 < 26.75)
ClCr, ml/min/1.73 m^2	98.4 (89.6 < 123.04)	39.8 (24.9 < 65.5)	124.8 (104.3 < 145.2)

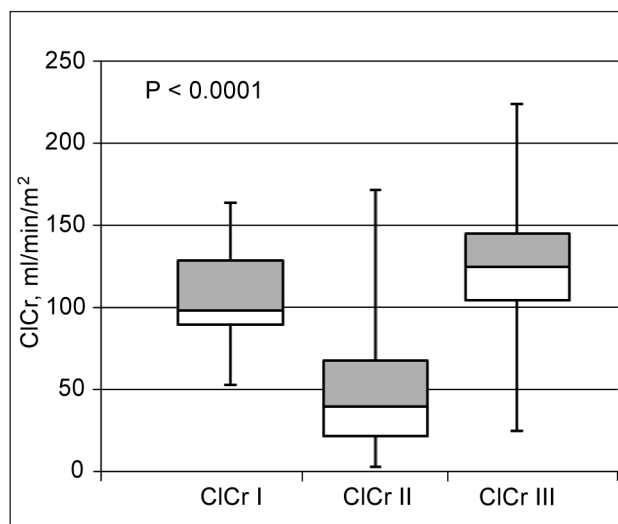**Fig. 1.** Changes in SCr

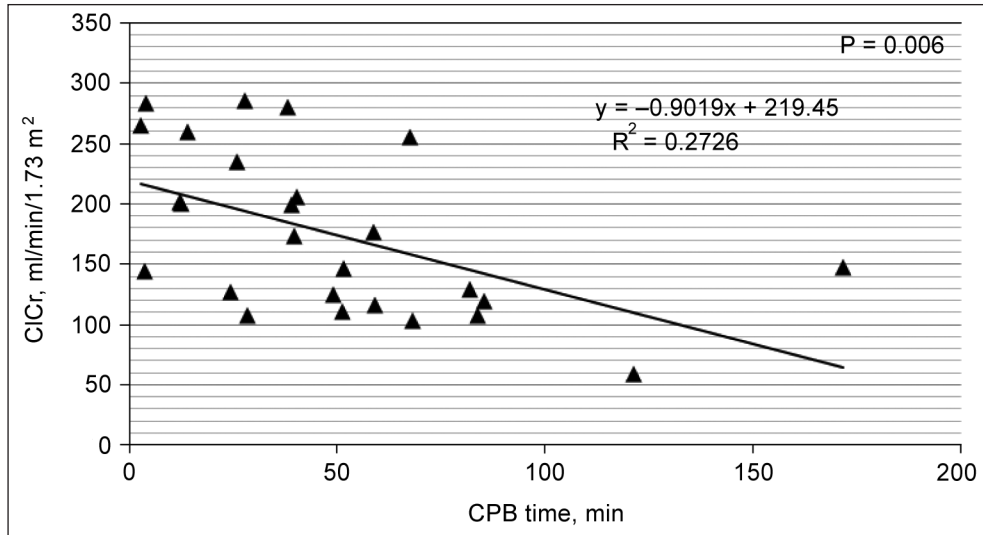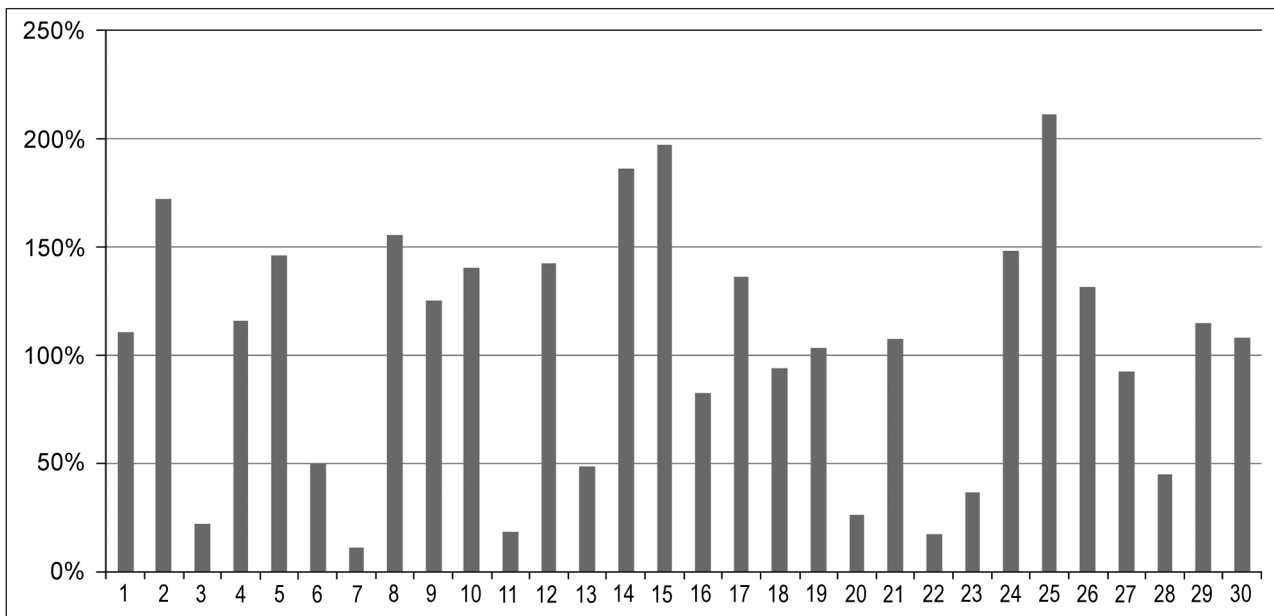**Fig. 2.** Changes in ClCr

Fig. 3. ClCr vs. CPB time

Fig. 4. Individual ClCr values expressed in % from the age norm

DISCUSSION

The etiology of AKI after CPB is multifactorial and incompletely understood. Various factors related to CPB have been implicated as possible determinants of AKI. They include hypothermia, hypoxia, hypotension, non-pulsatile blood flow during CPB, use of ACE inhibitors, inotropic and (or) vasoactive support that affect kidney and contribute to AKI. CPB is associated with significant hemodynamic changes, and the maintenance of cardiovascular stability during CPB requires interplay between the function of the CPB machine and patient factors,

such as systemic vascular resistance, venous compliance, and autoregulatory capacity of various vascular beds. The ultimate goal is to maintain regional perfusion at a level that supports the optimal cellular and organ function. Thus, any decrease in renal perfusion during CPB, depending on its magnitude and duration, can lead to significant cellular injury. The reported incidence of AKI after pediatric open heart surgery varies from 1.6% to 52% depending on the definition. To amend this variability, the Acute Dialysis Quality Initiative group standardized the definition of AKI in 2002 using the RIFLE criteria (17). Based on the glomerular filtration rate, serum

creatinine values, and urine output plotted against time of admission, RIFLE marks progressive degrees of injury in both intensive care unit and non-intensive care unit adult patients. In 2004, the Acute Kidney Injury Network defined AKI based on time in relation to the absolute creatinine increase, percentage increase, or documented oliguria. The adult-derived RIFLE definition was modified, applied, and validated in studies of critically ill patients (18) and renamed the pediatric RIFLE (pRIFLE) criteria (19). In the study conducted by Liu and colleagues (13) defined AKI was 50% or greater increase in serum creatinine from baseline within 3 days. Of the 71 pediatric patients undergoing open heart surgery, AKI developed in 20 patients (28%). In Krawczeski with coauthors' (12) study of 240 pediatric patients, AKI occurred in 27% of them. Patients having AKI were younger and had lower baseline SCr. None of their patients required RRT. AKI was associated with longer CPB times ($P = 0.0005$) and increased need for mechanical ventilation 33% versus 78% ($P = 0.006$) in patients having AKI. In Bennett's study (8) AKI developed in 99 patients (51%). Blinder with colleagues (9) retrospectively studied 430 infants who underwent heart surgery for congenital defects and observed AKI in 52% of patients. Even in the studies published after introduction of RIFLE and AKIN definitions, variability (27%–52%) of AKI incidence has been reported [5, 6, 8, 9, 15]. Our study was based on ClCr measurement which better reflects the glomerular filtration rate and is more accurate than SCr. The impact on renal biomarkers of CPB was more pronounced in ClCr in our study than in SCr changes. Raise in SCr was by 20.9% (median postoperative 35 μmol/l versus baseline 29 μmol/l) and drop in ClCr was 59.5% (median post operative 39.8 ml/min/1.73 m^2 versus baseline 98.4 ml/min/1.73 m^2) (Table 4, Figs. 1, 2). Our patients were classified by the creatinine-based pediatric modified RIFLE (pRIFLE) criteria for AKI, which have been using the changes in measured ClCr. It is difficult to compare SCr and ClCr values of various ages due to a wide distribution of specific values. ClCr vary from 17 ml/min/1.73 m^2 in the first week of life to 157 ml/min/1.73 m^2 at 12 months of age (20). These age-related variations are ignored in many studies where patients of various ages have been enrolled. To overcome this difficulty, we narrowed the inclusion criteria (body weight less than 10 kg). To compare patients of different ages during

data processing, we expressed individual ClCr values in % of the age norm (Fig. 4). According to pRIFLE criteria (50% decrease in ClCr), we detected in 30% (9/30) of our patients compliance with AKI. Both classifications rely heavily on SCr, which, by itself, is not an ideal biomarker for AKI. However, in current clinical practice, the gold standard for identification and classification of AKI is dependent on serial SCr measurements. In last years, a number of new, more sensitive biomarkers of kidney injury are introduced, tested and validated (21). Kidney injury molecule-1, interleukin-18, and liver fatty acid-binding protein (L-FABP) have been shown to be associated with kidney ischemia (13). Clinical studies indicate urine and serum neutrophil gelatinase-associated lipocalin as highly sensitive, specific, and predictive of AKI in many different disease processes (14). Despite the enthusiasm with novel biomarkers, most of them are still not available for routine clinical practice. In the postoperative care ClCr based estimate of GFR still may be a good biomarker of change in the renal function (22). Until recently, most AKI studies have focused on critically ill children who receive some form of RRT. Meanwhile, care for the critically ill child with AKI has improved greatly, with survival rates reaching 60–70% for children who require renal replacement therapy (23). Few data exist to describe the long-term outcomes of survivors of a pediatric AKI episode. Finally, at 3- to 5-year follow-up, 40% to 50% of pediatric patients who had AKI show signs of chronic renal insufficiency, indicating that sublethal injury permanently alters the renal bed (24). To evaluate outcome of AKI in our patients, we used ClCr based pRIFLE criteria. We observed normalization of both biomarkers (SCr and ClCr) before discharging patient from the hospital. Evidence supports an independent association between the duration of CPB and the development of CPB related AKI (25). In general, the longer the duration of extracorporeal support, the higher the risk of coagulopathy, the need for transfusion support, gut hypoperfusion, renal ischemia and AKI. There is no single defined threshold time during CPB beyond which the incidence of AKI increases dramatically. Future studies may better define a safe time limit during CPB to decrease AKI-CPB. In our study we find statistically significant ($P = 0.006$) inverse correlation ($r = –0.522$) between CPB time and ClCr (Fig. 4).

CONCLUSIONS

Open heart surgery is associated with a high risk for developing AKI. This complication is associated further with substantial morbidity and mortality. The pathogenesis of kidney injury during CPB is complex and involves hemodynamic, inflammatory, and other mechanisms that interact at a cellular level. At present, no pharmacologic interventions have demonstrated conclusively the efficacy in the prevention of renal dysfunction after cardiac surgery. More important is to prevent development of AKI preserving autoregulation of renal perfusion to avoid ischemic injury. The incidence of AKI in our group of patients was 30% (9/30), however, the category of AKI did not require application of any form of RRT. We find a statistically significant ($P = 0.006$) inverse correlation ($r = 0.522$) between CPB time and ClCr. Short-time outcome (less than one month) shows that in the population studied these changes have a severe, but transient effect and renal biomarkers (SCr and ClCr) return to normal values at the time of discharging the patient from hospital.

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VAIKŲ SERGAMUMAS ŪMIU INKSTŲ PAŽEIDIMU IR JO IŠEITYS PO ATVIRŲ ŠIRDIES OPERACIJŲ

Santrauka

Įvadas. Širdies operacijos su dirbtine kraujo apytaka (DKA) dažnai yra vertinamos kaip inkstų funkciją pabloginantis veiksnys. Hipotermija, hipoksija, hipotenzija ir nepulsuojanti kraujo tėkmė DKA metu, AKF inhibitorių naudojimas, inotropinė ir (ar) vazoaktyvi terapija paveikia inkstus ir prisideda prie ūmaus inkstų pažeidimo (ŪIP).

Tikslas. Įvertinti vaikų, kuriems buvo atliktos atviros širdies operacijos, sergamumą ŪIP ir išeitis.

Raktažodžiai: ūmus inkstų pažeidimas, inkstų biožymenys, kreatinino klirensas, atviros širdies operacijos vaikams