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The Effect of Cardiopulmonary Bypass Duration on Renal Injury after Congenital Heart Surgery in Infants and Young Children

Wpływ czasu trwania krążenia pozaustrojowego na uszkodzenie nerek po leczeniu chirurgicznym wrodzonych wad serca u niemowląt i małych dzieci

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Background. Improvements in surgical techniques and perioperative management mean that more complex cardiac procedures are being performed on very young patients.
Objectives. The aim of this study is to evaluate the effects of the duration of cardiopulmonary bypass (CPB) on renal injury after congenital heart surgery in infants and young children.
Material and Methods. 58 children with ages ≤ 3 years undergoing CPB surgery were divided into three groups according to the duration of their CPB: Group I was < 90 min, n = 15; Group II, 90–149 min, n = 25; and Group III was ≥ 150 min, n = 18. Urinary neutrophil gelatinase-associated lipocalin, interleukin-18, microalbumin and α1-microglobulin were measured at baseline and 4 h, 6 h, 12 h and 24 h after surgery.
Results. No significant differences were noted among the groups in terms of gender, age, weight and baseline serum creatinine. The incidence of acute kidney injury (based on serum creatinine increase) after surgery were 13.3% (2/15) in Group I, 52.0% (13/25) in Group II and 77.8% (14/18) in Group III. 4 children developed acute renal failure (ARF) requiring peritoneal dialysis; all of them were in Group III. The levels of urinary biomarkers increased significantly, peaked at 4 h and remained elevated up to 24 h after surgery. Group III had significantly higher levels of urinary biomarkers than Groups I and II at 4–12 h after surgery, while the levels were not significantly different at 24 h.
Conclusions. Prolonged CPB duration was related to more severe renal tubular injury and acute renal failure. Measurements of urinary kidney specific biomarkers in infants and children with a CPB duration of more than 150 min might help identify those at high risk for ARF **(Adv Clin Exp Med 2013, 22, 5, 693–698).**

Key words: renal injury, cardiopulmonary bypass, congenital heart surgery, infants and young children.

Słowa kluczowe: uszkodzenie nerek, krążenie pozaustrojowe, leczenie chirurgiczne wrodzonych wad serca, niemowlęta i małe dzieci.

Renal injury is a well recognized potential complication in infants and young children with congenital heart disease (CHD) following cardiopulmonary bypass (CPB) surgery [1, 2]. The spectrum varies from subclinical injury to acute renal failure (ARF) requiring peritoneal dialysis (PD). ARF has been reported to affect 1.6–32.8% of children after congenital heart surgery, with a high mortality of 20–79% [3]. Early prediction of postoperative renal injury could help practitioners better evaluate

the risk of ARF and to initiate early interventional or precautionary measures [4, 5]. With improvements in surgical techniques and perioperative management, more complex procedures are being performed on very young patients, with a prolonged CPB duration [6]. However, the effects of the duration of CPB on renal injury has not been extensively studied in this very young population.

One method of quantifying renal injury is measurement of kidney-specific biomarkers. Traditional markers such as serum creatinine are not sensitive enough to detect discrete and subclinical renal injury. Recent studies have revealed several novel and promising urinary biomarkers for the early diagnosis of acute kidney injury (AKI). Neutrophil gelatinase-associated lipocalin (NGAL) is a 25-kDa protein normally expressed at very low levels in kidneys [7]; interleukin-18 (IL-18) is a proinflammatory cytokine and biologically inactive precursor [8]. Expressions of both of these are markedly induced and activated in injured tubular cells in response to acute insults, and they excrete to a notable extent into the urine [7–9]. Another marker is α1-microglobulin (α1-MG), a low-molecular-weight protein that freely filters through the glomerulus and is reabsorbed mostly by proximal tubular cells. In the case of renal injury, urinary α1-MG excretion increases as an index of renal tubular dysfunction. Elevated urinary microalbumin (MA) reflects increased permeability of the basal membrane as a consequence of glomerular injury.

The aim of the present study is to use urinary biomarkers to evaluate the effect of CPB duration on renal injury after congenital heart surgery in infants and young children.

Material and Methods

Subjects

From November 2010 to April 2011, the authors prospectively enrolled all CHD children aged ≤ 3 years undergoing CPB surgery at Beijing Anzhen Hospital. Patients with congenital abnormalities of the urological system, known kidney disease, preoperative renal failure, malignant tumors, perioperative use of nephrotoxic drugs or recent radiocontrast exposure were excluded. 58 children (39 males and 19 females) fulfilled the inclusion criteria and constituted the study population. Written informed consent was obtained from the parents or legal guardian of each child.

The study population was divided into three graded groups according to their CPB duration: Group I was < 90 min, n = 15; Group II, 90–149 min, n = 25; and Group III was ≥ 150 min, n = 18. During cardiac procedures, the mean systemic arterial pressure was maintained at 50–70 mmHg. After surgery, intravenous vasoactive drugs (e.g. dopamine) were used to maintain blood pressure for adequate perfusion of vital organs. Milrinone was indicated on a short-term basis for impaired cardiac function, and diuretics for reduced urine output despite adequate volume state.

Sample Collection and Biomarker Measurement

Urine samples were collected at baseline and at 4 h, 6 h, 12 h and 24 h from the initiation of CBP. The samples were centrifuged at 2000 g for 10 min and stored the supernatants in two volumes at –4°C and –80°C respectively. Within 48 h of sampling urinary MA and α1-MG were measured using immunoturbidimetry at the clinical laboratory of Peking University First Hospital. Urinary NGAL and IL-18 were also measured, using commercially available ELISA kits for human NGAL (Quantikine, R&D Systems, Minneapolis, MN, USA) and IL-18 (MBL, Nagoya, Japan) at the central laboratory of Peking University People's Hospital. All the measurements were carried out in duplicates and averaged. Concentrations of biomarkers were expressed as ratios to urinary creatinine, in order to correct for urine volume variation. The medical staff was blind to the study design and laboratory results. Serum creatinine was measured routinely at baseline, then twice a day in the first 3 days after surgery and daily thereafter.

Statistical Analysis

The statistical analysis was performed using SPSS software, version 13.0 (Chicago, IL, USA). Normally distributed variables were expressed as mean ± standard deviation (SD), while non-normally distributed variables were expressed as median (interquartile range). Continuous variables were compared using a one-way ANOVA test or rank sum test. Categorical variables were displayed as percentages and compared using the χ^2 or Fisher exact test. A two-tailed P value of < 0.05 was considered to be statistically significant.

Results

Clinical Information

Table 1 summarizes the clinical characteristics and outcomes of the 3 groups. No significant differences were noted among the groups in terms of

gender, age, weight and baseline serum creatinine. Children with longer CPB duration had more complex cardiac surgical procedures as evaluated by Risk Adjustment for Congenital Heart Surgery 1 (RACHS-1) [10]. Patients with CPB < 90 min were all in RACHS-1 Category 2, while those with CPB ≥ 150 min were all in Categories 3–4. Urine output during the first 24 h after surgery was not significantly different among the groups. The incidences of AKI after surgery (defined as an absolute increase in serum creatinine ≥ 0.3 mg/dl [26.4 μmol/l], or a percentage increase ≥ 50% within a 72-hour period after surgery) were 13.3% (2/15) in Group I, 52.0% (13/25) in Group II, and 77.8% (14/18) in Group III. 4 children developed ARF requiring peritoneal dialysis, and were all in Group III. The procedures associated with ARF included repair of a coarctation and ventricular septal defect closure in a one-month-old infant, total repair of a tetralogy of Fallot with pulmonary atresia in two cases, and an arterial switch operation with ventricular septal defect closure in one.

Serial Measurements of Urinary Biomarkers

Table 2 shows the urinary biomarker measurements at baseline and various points in time after CPB surgery. The baseline levels of the urinary biomarkers were low and did not show significant differences among the groups. They increased markedly and peaked at 4 h, and remained elevated up to 24 h after surgery. The 4 h concentrations of urinary NGAL were significantly different among groups (Group I < Group II < Group III, $P < 0.05$). The 4 h concentrations of urinary IL-18, MA and α1-MG were significantly higher in Group III than in Groups I and II ($P < 0.05$). Group III also had significantly higher levels of urinary biomarkers than Groups I and II at 6–12h after surgery, while the levels were not significantly different at 24 h after surgery.

Discussion

CPB surgery is often complicated by renal injury. The pathophysiology is multifactorial, and related to perioperative renal hypoperfusion and the formation of endogenous and exogenous nephrotoxins and microembolisms [11, 12]. Clinical studies have proved that off-pump cardiac surgery is superior to on-pump procedures in adults with respect to postoperative renal injury [13, 14]. Compared with older patients, infants and young children are more susceptible to postoperative kidney damage and ARF [3, 15]. Young children are unique because they rarely have co-morbid conditions such as hypertension and diabetes, which are commonly present in adult patients and may have

Table 1. The patients' clinical characteristics in different groups

Items	CPB < 90 min (n = 15)	90–149 min (n = 25)	CPB ≥ 150 min (n = 18)
Males, n (%)	9 (60.0%)	15 (60.0%)	15 (83.3%)
Age (months)	9.3 ± 8.1	14.2±12.5	14.1 ± 14.0
Weight (kg)	7.2 ± 1.9	8.0 ± 3.2	7.4 ± 3.2
Serum creatinine (μmol/L)	36.7 ± 15.8	30.8 ± 9.8	33.3 ± 9.4
eGFR ($mL \cdot min^{-1} \cdot 1.73\ m^{-2}$)	90.3 ± 40.3	112.5 ±50.2	100.8 ± 45.1
RACHS-1			
Category 2, n (%)	15 (100%)	11 (44.0%)	0 (0)
Category 3, n (%)	0 (0)	12 (48.0%)	10 (55.6%)
Category 4, n (%)	0 (0)	2 (8.0%)	8 (44.4%)
Urine output during the first 24 h postoperatively ($mL \cdot kg^{-1} \cdot h^{-1}$)	3.5 ± 1.5	3.4 ± 1.4	4.0 ± 1.5
ICU hospital stay (days)	4.6 ± 2.4	7.0 ± 4.4	7.6 ± 6.4
AKI, n (%)	2 (13.3%)	13 (52.0%)	14 (77.8%)
ARF requiring PD, n (%)	0 (0)	0 (0)	4 (22.2%)

AKI – acute kidney injury, ARF – acute kidney injury, CPB – cardiopulmonary bypass duration, ICU – intensive care unit, PD – peritoneal dialysis, RACHS-1 – Risk Adjustment for Congenital Heart Surgery 1.

Table 2. Urinary biomarker measurements at baseline and various times after CPB surgery

	Baseline	4 h	6 h	12 h	24 h
NGAL/UCr (ng/mg)					
CPB < 90 min (n=15)	9.5 (4.0–18.0)	46.3 (8.3–207.4) #	34.0 (11.0–92.1)	15.8 (7.3–42.6)	16.7 (9.6–45.9)
90–149 min (n = 25)	12.1 (4.5–29.1)	695.7 (22.5–3799.5) #	85.9 (10.9–261.4)	20.5 (7.2–70.8)	34.3 (12.6–77.2)
CPB ≥ 150 min (n = 18)	6.6 (1.6–40.4)	2881.4 (813.0–10303.2)*	962.2 (102.1–2884.0)*	76.3 (49.9–933.0)*	24.2 (15.3–101.7)
IL-18/UCr (pg/mg)					
CPB < 90 min (n=15)	135.7 (31.1–324.6)	890.0 (230.5–1912.0)	417.0 (110.0–1301.0)	244.7 (136.2–640.0)	195.6 (51.8–491.3)
90–149 min (n = 25)	65.7 (15.6–142.3)	1140.2 (318.7–3045.8)	445.7 (225.0–1033.3)	320.6 (82.7–474.2)	118.9 (69.9–274.0)
CPB ≥ 150 min (n = 18)	56.9 (4.3–315.3)	5060.4 (1540.8–9197.9)*	2238.9 (615.8–6273.8)*	468.9 (249.5–1512.2)*	234.6 (68.7–695.0)
MA/UCr (mg/g)					
CPB < 90 min (n=15)	23.3 (13.9–50.5)	119.0 (51.4–723.3)	87.2 (66.0–263.1)	86.5 (39.5–166.0)	115.8 (64.2–183.0)
90–149 min (n = 25)	30.5 (16.5–59.3)	537.6 (59.8–1931.4)	159.1 (39.2–723.6)	94.9 (66.6–150.1)	92.6 (63.6–211.4)
CPB ≥ 150 min (n = 18)	25.4 (19.0–46.0)	1683.5 (483.9–4147.8)*	404.4 (254.0–2141.1)*	220.8 (68.8–926.9)*	233.7 (66.5–564.2)
α1-MG/UCr (mg/g)					
CPB < 90 min (n=15)	36.0 (10.7–68.0)	154.0 (64.3–283.4)	98.9 (32.2–353.6)	30.8 (24.3–132.1)	57.6 (33.6–160.7)
90–149 min (n=25)	25.5 (12.5–59.9)	469.1 (101.4–1108.2)	116.9 (35.9–402.7)	40.5 (25.7–113.9)	68.7 (33.7–97.0)
CPB ≥ 150 min (n = 18)	29.5 (15.4–72.7)	922.2 (386.3–1871.1)*	449.4 (213.7–1105.6)*	137.5 (94.6–330.2)*	101.0 (34.0–216.7)

NGAL – neutrophil gelatinase-associated lipocalin, IL-18 – interleukin-18, MA – microalbumin, α1-MG – α1-microglobulin, UCr – urinary creatinine. Values are expressed as medians with the interquartile range.

* indicates a significant difference ($p < 0.05$) from the other groups, and # indicates a significant difference between two groups.

detrimental effects on postoperative renal function. Therefore, young children constitute an ideal population to study the effects of CPB duration on renal injury after cardiac surgery.

To quantitatively assess renal injury, the authors measured urinary biomarkers that have been found to be sensitive and reliable indicators for that purpose. Urinary diagnostics have the additional advantage of being non-invasive in nature. The current study showed significant alteration in kidney-specific biomarkers early after surgery. The increase of urinary NGAL, IL-18 and α1-MG levels clearly suggested tubular injury after CPB surgery. As tubular dysfunction can also cause microalbuminuria owing to decreased reabsorption of filtered albumin [16], urinary MA levels must be at least 5–6 times of α1-MG to indicate glomerular injury [17, 18]. Therefore, the increase of urinary MA found in this study did not actually suggest glomerular damage because of the similar levels of the two markers.

The authors divided the study population into 3 graded categories based on CPB duration. As shown in Table 1, longer CPB durations were positively correlated with higher RACHS-1 categories. The study showed that prolonged CPB duration was related to more severe renal injury and ARF. These results were in agreement with studies on adults, which showed that patients with CPB times over 90 min had more pronounced kidney damage than patients with CPB times under 70 min [19]. Previous retrospective studies also identified longer CPB duration as a potential clinical risk factor for ARF after congenital heart surgery [3]. The current study supplemented the results of these studies and demonstrated that CPB duration was positively correlated with the degree of renal injury after surgery even without the development of ARF, as shown in urinary biomarker levels at 4 h after surgery. This positive relationship might be due to longer renal ischemic time and more severe ischemia-reperfusion injury. Additionally, a more intense systemic inflammatory response might also play a prominent role, as demonstrated by higher IL-18 levels with longer CPB duration [12].

In the present study, 4 patients developed postoperative ARF requiring PD, and all 4 of them had CPB durations over 150 min. As children with postoperative ARF have a high mortality rate [3], early and accurate prediction immediately after surgery is essential for early treatment and good clinical outcomes. Recent studies have revealed several novel urinary biomarkers which alone or in combination might be promising candidates in the early diagnosis of ARF [7, 8]. Measurements of these urinary biomarkers in patients with CPB duration ≥ 150 min might be cost-effective and confirmative in the early prediction of ARF. However, the authors cannot compare their predictive capacities or establish the optimal predictive panel of biomarkers for ARF in this study due to the small sample size and very few children with ARF. Future large-scale studies are needed to address this issue.

Conclusions

In summary, prolonged CPB duration was related to more severe renal injury and ARF. Measurements of urinary kidney specific biomarkers in infants and children with CPB duration over 150 min might help identify those at high risk for ARF.

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