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Pre-operative levels of urinary uromodulin predict acute kidney injury after pediatric cardiopulmonary bypass surgery

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Abstract

Background—Acute Kidney Injury (AKI) is a common complication of cardiopulmonary bypass surgery (CPB) in children. Several promising post-operative AKI biomarkers have been identified, but no pre-operative biomarkers are available. We evaluated the association of urinary uromodulin (uUMOD) with post-operative AKI.

Methods—101 children undergoing CPB were enrolled. Urine was collected prior to CPB. AKI was defined as $\geq 50\%$ increase in serum creatinine from pre-operative baseline within 48h of surgery.

Results—Forty-seven patients (47%) developed AKI. 92% of participants in the lowest quartile of pre-operative uUMOD concentrations developed AKI, compared to 8% in the highest quartile. Patients with pre-operative uUMOD levels in the lowest quartile had 132.3 times increased risk of post-operative AKI versus the highest quartile. Raw uUMOD levels were significantly lower in patients with AKI vs. no AKI. Significance was unchanged after correcting uUMOD levels for urinary creatinine. Receiver operating characteristic analysis showed pre-operative uUMOD strongly predicted post-operative AKI with area under the curve (AUC) 0.90. Stepwise logistic regression analysis revealed a model combining uUMOD and bypass time predicted AKI with $p < 0.001$. Neither RACHS Score nor age improved the model's ability to predict AKI. Independent analysis demonstrated that while bypass time was associated with AKI, the predictive ability of bypass time (AUC 0.77) was less than that of pre-operative uUMOD levels (AUC 0.9).

Conclusions—Children with lowest pre-operative levels of uUMOD have greatly increased risk of AKI post CPB. If uUMOD were used to risk stratify patients undergoing CPB, clinical measures could be taken to minimize AKI development.

Keywords

Acute Kidney Injury (AKI); Cardiopulmonary Bypass Surgery (CPB); Biomarker; uromodulin (UMOD); Tamm-Horsfall Protein (THP)

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Disclosures

None

Introduction

Acute kidney injury (AKI) is a common and serious complication of cardiopulmonary bypass surgery (CPB), occurring in up to 50% of pediatric patients undergoing the procedure [1, 2]. Depending on the definition of AKI used, the mortality rate ranges between 20% and 79% [1, 3]. Risk factors for AKI after CPB include age <2 years, history of prior surgeries, and longer bypass time [1, 4, 5].

Much research has been dedicated to the discovery of postoperative biomarkers to predict AKI and its severity. Proteins that mark tubular damage, such as neutrophil gelatinase-associated lipocalin (NGAL), interleukin 18 (IL-18) and kidney injury molecule-1, have shown promise as potential early diagnostics of AKI [6–11]. However, there are currently no pre-operative measures in use to determine a patient's predisposition to developing AKI after CPB. Recent studies have demonstrated that lower urinary excretion of uromodulin (UMOD), also known as Tamm-Horsfall Protein (THP), measured in adult patients prior to CPB, is associated with higher odds of developing AKI post-surgery [12].

UMOD is the most abundant protein excreted in urine. It is a glycoprotein that is expressed in the thick ascending limb (TAL) of the Loop of Henle and was first purified by Igor Tamm and Frank Horsfall in 1952 [13–15]. Mutations in the *UMOD* gene are associated with medullary cystic kidney disease and autosomal dominant tubulointerstitial kidney disease [16, 17]. In healthy kidneys, UMOD is thought to have a role in salt transport in the tubules, innate immunity and protection against kidney stones [18].

In this study, we set out to determine if pre-operative levels of urinary UMOD are associated with risk of AKI in a cohort of pediatric patients undergoing CPB.

Methods

Patients

This study was approved by the Cincinnati Children's Hospital Medical Center Internal Review Board and was carried out in accordance with the Declaration of Helsinki. All patients <18 years of age undergoing cardiac surgery with CPB at our center between June 2005 and July 2007 were approached for study inclusion. Written informed consent was obtained from the legal guardian of each patient, and assent was obtained from patients aged 11 years and older at the time of enrollment. Patients with pre-existing renal insufficiency (serum creatinine (SCr) >2 times age-adjusted normal range) were excluded. Past nephrotoxin use, such as contrast or aminoglycoside, was not an exclusion factor as long as the SCr was normal at the time of surgery. Complexity of surgery was categorized according to the Risk Adjustment for Congenital Heart Surgery 1 (RACHS-1) scoring system [19]. Urine samples for biomarker analysis were obtained immediately before CPB and stored in aliquots at –80°C. SCr was measured at baseline, immediately after surgery and at least daily in the post-operative period.

The primary outcome measure was AKI, defined as a 50% or greater increase in SCr above pre-procedural baseline within 48 hours post-surgery, comprising modified KDIGO criteria [20]. Secondary outcomes included bypass time and length of hospital stay.

Biomarker measurements

Urinary UMOD was measured using a clinically available ELISA kit, per manufacturer's instructions (EHUMOD, Thermo-Fisher Scientific, Waltham, MA). Intra- and inter-assay variability were 10% and 12%, respectively. Urine creatinine was measured using an enzymatic creatinine assay on a Dimension RXL clinical analyzer (Siemens, Munich, Germany). Coefficients of variability for the creatinine measurements were 2.4% (intra) and 4.2% (total).

Statistics

Statistical analysis was performed using SigmaPlot 12.5 (Systat Software, Inc., Chicago, IL). Demographics, baseline measurements and clinical outcomes were summarized and compared between AKI and no AKI patients. For continuous variables, median and inter-quartile ranges (IQR) were reported and Wilcoxon rank sum test was used to test for group differences. For categorical variables, frequencies and proportions were reported and Chi-square test or Fisher's exact test was used to test for group differences. For UMOD measurements, median and IQR were calculated and subjected to Mann-Whitney Rank Sum Analysis. UMOD IQR was used to categorize patients into quartiles to calculate odds ratios for development of AKI. To determine association of clinical variables and UMOD levels with AKI, a stepwise logistic regression analysis was performed. Independent receiver operator characteristic curves (ROC) were also calculated for each variable (UMOD, length of stay, RACHS score and bypass time), and the area under the curve (AUC) was calculated to determine the discriminatory power for each variable to predict AKI. In all tests, p-values 0.05 were considered significant.

Results

Patient characteristics

One-hundred and one patients <18 years of age undergoing on-pump cardiac surgery at our center were enrolled in this prospective study. Forty seven (47%) developed AKI. Patient demographic and clinical characteristics can be found in Table 1. There were no differences between AKI and non-AKI patients in terms of age, sex, race, prior CPB or RACHS score. Bypass times and length of hospital stay were significantly increased in AKI patients ($p < 0.001$).

uUMOD and AKI

Table 2 shows that 92% of the participants in the lowest quartile of urinary UMOD levels developed AKI, compared to 8% in the highest quartile. Odds ratios demonstrated that having a uUMOD level in the lowest quartile yielded a 132.3 times increased risk of developing AKI vs. the highest quartile. Raw UMOD levels were significantly lower in patients with AKI (4.739 μ g/ml; 25th 2.454; 75th 6.483) vs. no AKI (13.701 μ g/ml; 9.022, 20.999) (Figure 1a). Significance did not change with urine creatinine correction (Figure

1b). ROC analysis of pre-operative uMOD levels demonstrated an AUC of 0.90 for prediction of AKI ($p < 0.001$) (Figure 2). Stepwise logistic regression analysis revealed that a model combining UMOD (F statistic 33) and bypass time (F statistic 32) could predict AKI with a $p < 0.001$. Neither RACHS Score (F statistic 2.1, $p = 0.15$) or age (F statistic 1.6, $p = 0.2$) added to the ability of the model to predict AKI. Independent analysis demonstrated that while bypass time was associated with AKI, the predictive ability of bypass time AUC (0.77) was less than that of the pre-operative urinary UMOD levels (AUC 0.90) (Figure 2).

uMOD and nonrenal outcomes

Lower pre-operative concentrations of uMOD were also associated with a longer length of hospital stay ($r = -0.31$, $p = 0.002$) (Figure 3).

Discussion

This is the first study to show that lower pre-operative levels of urinary UMOD in children undergoing CPB is associated with increased risk of AKI. We found that raw UMOD levels were significantly lower at baseline ($p < 0.001$) in patients who developed AKI after CPB than those who did not develop AKI. In fact, we found that patients in the lowest quartile of baseline UMOD concentrations had a 132.5 times increased odds of developing AKI post-surgery than those patients in the highest quartile. While increased bypass time was also associated with AKI (AUC 0.77), baseline urinary UMOD levels were more predictive of AKI (AUC = 0.90), independent of complexity of surgery or age. We also found that baseline urinary UMOD levels were negatively associated with the length of hospital stay, likely due to increased incidence of AKI in patients with low baseline UMOD levels.

AKI is a common and serious complication of CPB in both children and adults. It occurs at a high rate in children (20–60%) and is associated with higher in hospital mortality and increased length of stay [20–22]. Due to the complications associated with AKI, it is also associated with a significant financial burden. In the United States, it is estimated that AKI accounts for increased hospitalization costs of \$5.4 – 24 billion annually [23]. In the adult population, AKI after CPB is associated with increased risk of CKD and hypertension [24, 25]. In the pediatric population, higher incidences of CKD and hypertension at 5 years following CPB have been identified [21].

The production of UMOD is restricted to the TAL of the Loop of Henle and the most proximal portion of the distal tubule [26]. UMOD is a glycoprotein with the capability of binding to a large number of ligands [27]. UMOD has been shown to bind to cells, immunoglobulins, cytokines, crystals and ions. One of the physiological roles proposed for UMOD is to bind harmful products to remove them from the tubular fluid [28]. UMOD is typically associated with the apical membrane domain of the TAL, but has been shown in mice to translocate to the basolateral domain of the TAL, the interstitium and the S3 segment of proximal tubules in the recovery period post AKI [29]. This was hypothesized to contribute to potential cross-talk between the TAL and the S3 segment to downregulate inflammatory molecules in proximal tubules. The authors demonstrated that in a mouse model of ischemia reperfusion injury, the S3 tubular cells in UMOD deficient mice expressed a high level of Macrophage inflammatory protein (MIP-2) - a neutrophil-attracting

chemokine – and were surrounded by neutrophils. It is thought that the basolateral translocation of UMOD interacts with the S3 segments to reduce expression of MIP-2 and therefore decrease damage due to inflammation in the tubules [30].

Our data is consistent with earlier studies in both adults and neonates. Garimella et al. [12], found that lower pre-surgery levels of uUMOD in adults undergoing on-pump cardiac surgery had increased odds of AKI, but the significance of the data in their population was not as strong as ours, and more evident in cases of severe AKI. They also demonstrated that lower pre-surgery uUMOD was inversely related to peak SCr post-surgery. This is consistent with the idea that UMOD has a protective effect on renal tubules. The slight differences in our results could be due to a number of variables. First, children have fewer comorbid conditions than adult patients, rendering biomarkers in children being subjected to fewer confounding variables. Secondly, the ELISA kit used by Garimella et al. [12] was discontinued by the manufacturer, necessitating a different kit for our analysis. Similarly, Askenazi, et al. [31] demonstrated 62% lower levels of uUMOD in critically-ill neonates with AKI than in those without. In this setting it was not predictive, since the children already had AKI, but had a good discriminatory value (AUC 0.77) to distinguish AKI from non-AKI patients.

Our study has several strengths. We used a well characterized patient cohort that has been useful in evaluating the predictive value of tubular markers to predict AKI post-surgery [9]. While we used a different commercially available ELISA kit than in previous studies [12, 32], the results from the kit used in this study correlated well with the referenced kit (data not shown). To our knowledge, this is the first study to assess pre-operative levels of uUMOD in an attempt to determine AKI risk in pediatric patients undergoing CPB. Our results were consistent with adult studies, but had a much higher degree of significance ($p=0.03$ in adults vs 0.001 in our study) [12]. We also determined that the association of urinary UMOD with AKI (AUC = 0.90) was independent of age, RACHS score or bypass time.

Our study is not without limitations. This was a single center study with a relatively small sample size. As such, we were not able to stratify patients by severity of AKI. Stratification of AKI by pRIFLE criteria, for instance, could be informative to determine whether there is a direct correlation between uUMOD levels and AKI severity. Lastly, our samples had been stored at -80°C for 10 years at the time of our analysis. Studies have shown that storage of urine for greater than 8 months does yield a small, but significant decrease in uromodulin as measured by ELISA [33], but there is no reason to expect that this decrease would be influenced differentially in samples from patients with AKI vs their non-AKI counterparts.

In conclusion, assessment of risk factors prior to CPB in children, including urinary UMOD levels, could allow physicians to implement strategies to reduce AKI risk and improve overall outcomes for these patients. While this concept needs further exploration in a larger multi-center cohort to allow further validation and stratification for AKI severity, combining pre-operative risk assessment with post-operative monitoring of tubular damage markers such as NGAL could yield significant improvement in the care of CPB patients.

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Figure 1.

a) Raw UMOD levels were significantly lower in patients with AKI (4.739 µg/ml; 25th 2.454; 75th 6.483) vs. no AKI (13.701 µg/ml; 9.022, 20.999) b) Significance did not change with urine creatinine correction. uMOD – urinary uromodulin; AKI – acute kidney injury; Cr – creatinine.

ROC Curves

Figure 2.

ROC curve analysis of uUMOD and bypass time for discrimination of AKI. The AUC for uUMOD was 0.90 vs 0.77 for Bypass time. Both values reached statistical significance ($p = 0.001$). uUMOD – urinary uromodulin; AKI – acute kidney injury; ROC – receiver operating characteristic; AUC – area under the curve.

Figure 3.

Association of uUMOD with Non-Renal Outcomes. Spearman correlation showed that uUMOD was negatively correlated with length of hospital stay. ($r = -0.31$, $p = 0.002$). uUMOD – urinary uromodulin.

TABLE 1**PATIENT CHARACTERISTICS**

Characteristics	No AKI n = 54	AKI n = 47	p value
Age, years	3.9 (0.7–6.6)	1.8 (0.5–5.3)	0.17
Male	30 (55.6)	26 (55.3)	0.86
White race	48 (88.9)	42 (89.4)	0.81
Prior CPB	32 (59.2)	19 (40.4)	0.09
Bypass time, minutes	93 (67.0–114.5)	152 (103.0–182.0)	< 0.001 *
Hospital stay, days	4 (3.0–6.0)	7 (5.0–13.0)	< 0.001 *
Rachs score			0.65
1	7 (13.0)	7 (14.9)	
2	26 (48.1)	25 (53.2)	
3	18 (33.3)	13 (27.7)	
4	2 (3.7)	0 (0)	
5	1 (1.9)	1 (2.1)	
6	0 (0)	1 (2.1)	

Values are median (interquartile range) for continuous variables (with p values from Wilcoxon rank sum test) or n (%) for categorical variables (with p values from chi-square test or Fisher exact test).

* deems significance $p < 0.05$.

AKI – acute kidney injury; CPB – cardiopulmonary bypass.

Table 2

uMOD ug/ml	N (%) of AKI events	Odds Ratios (vs Q4)	95% CI	p value
Total	47 (46.5)			
Q1: < 4.6	23 (92.0)	132.3	17.1–1020.5	< 0.001 *
Q2: 4.6–8.5	17 (65.3)	21.7	4.1–113.7	< 0.001 *
Q3: 8.51–14.4	5 (20.0%)	2.9	0.5–16.4	0.42
Q4: >14.4	2 (8.0%)			

Odds Ratios to develop AKI based on quartile (Q) level of urinary UMOD.

* deems significance $p < 0.05$.

AKI acute kidney injury, uMOD urinary uromodulin.