CONGENITAL HEART

Lack of Furosemide Responsiveness Predicts Acute Kidney Injury in Infants After Cardiac Surgery

Aadil Kakajiwala, MBBS,* Ji Young Kim, PhD, John Z. Hughes, MPH, Andrew Costarino, MD, MSCE, John Ferguson, J. William Gaynor, MD, Susan L. Furth, MD, PhD, and Joshua J. Blinder, MD

Department of Pediatrics, Division of Pediatric Nephrology, Washington University in St. Louis School of Medicine, St. Louis, Missouri; Department of Pediatrics, Division of Nephrology, and Clinical Translational Research Center, Children's Hospital of Philadelphia; College of Medicine and Dornsife School of Public Health, Drexel University; Department of Anesthesia and Critical Care Medicine, Division of Cardiac Critical Care, and Department of Surgery, Division of Cardiothoracic Surgery, Children's Hospital of Philadelphia; and Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

Background. **This was a retrospective study to determine whether lack of furosemide responsiveness (LFR) predicts acute kidney injury (AKI) after cardiopulmonary bypass surgery in infants.**

Methods. **Infants (less than 1 year of age) undergoing cardiopulmonary bypass surgery, receiving routine postoperative furosemide (0.8 to 1.2 mg/kg per dose between 8 and 24 hours after surgery) were included. Urine output was measured 2 and 6 hours after furosemide dose. Lack of furosemide responsiveness was defined a priori as urine output less than 1 mL · kg^{-1} · h^{-1} after furosemide. Serum creatinine was corrected for fluid balance. Acute kidney injury was determined using changes in uncorrected and corrected serum creatinine. The predictive utility of LFR was assessed using receiver-operating characteristics curve analysis.**

Results. **We analyzed 568 infants who underwent cardiopulmonary bypass. Eighty-one (14.3%) had AKI using uncorrected serum creatinine; AKI occurred in 41 (7.2%) after correcting for fluid overload. Patients with AKI had a lower response to furosemide (median urine output 2 hours: 1.2 versus 3.4 mL · kg^{-1} · h^{-1}, $p = 0.01$; median urine output 6 hours: 1.3 versus 2.9 mL · kg^{-1} · h^{-1}, $p = 0.01$). After creatinine correction, LFR predicts AKI development (area under receiver-operating characteristics curve of 0.74 at 2 hours and 0.77 at 6 hours). After adjusting for surgical complexity using The Society of Thoracic Surgeons/European Association for Cardiothoracic Surgery mortality categories, the area under the receiver-operating characteristics curve was 0.74 at 2 hours and 0.81 at 6 hours. Patients with urine output greater than 1 mL · kg^{-1} · h^{-1} were unlikely to have AKI (negative predictive value, 97%).**

Conclusions. **After correcting serum creatinine for fluid balance and adjusting for surgical complexity, LFR performs fairly at 2 hours, whereas at 6 hours, LFR is a good AKI predictor. Prospective studies are needed to validate whether diuretic responsiveness predicts AKI.**

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Cardiac surgery-associated acute kidney injury (AKI) occurs frequently and is associated with increased mortality risk, longer intensive care unit and hospital length of stay, and need for prolonged mechanical ventilation [1, 2]. Infants may be at particularly high risk of AKI after cardiac surgery, with injury occurring in as many as 64% of infants postoperatively [3–5]. Current definitions for AKI use either urine output or serum creatinine [6–10]. In 2012, the Kidney Disease Improving Global Outcome (KDIGO) AKI criteria integrated several AKI definitions into a single methodology to define and stage AKI [6]. The KDIGO criteria have been modified for neonates and young infants (aged less than 120 days) using an absolute rise in serum creatinine to stage AKI [7].

Furosemide is a loop of Henle diuretic that enters the tubular lumen by active secretion [11]. In patients with AKI, the diuretic effect of furosemide is blunted because

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Address correspondence to Dr Kakajiwala, Department of Pediatrics, Division of Pediatric Nephrology, Washington University in St. Louis School of Medicine, Campus Box 8116, 660 Euclid Ave, St. Louis, MO 63110; email: kakajiwala_a@kids.wustl.edu.

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Abbreviations and Acronyms

AKI = acute kidney injury
AUC = area under the curve
CI = confidence interval
IQR = interquartile range
KDIGO = Kidney Disease Improving Global Outcome
LFR = lack of furosemide responsiveness
ROC = receiver-operating characteristics
STAT = The Society of Thoracic Surgeons/European Association for Cardiothoracic Surgery

of reduced tubular secretion. Hence, response to furosemide, in terms of urine output, may be a good indicator of renal tubular function.

Chawla and associates [12] investigated whether diuretic responsiveness (furosemide stress test) could be used to predict AKI progression in a cohort of critically ill adults. In patients with AKI, hourly urine output at 2 hours was significantly lower than noted in patients who did not progress. Urine output 2 hours after furosemide predicted AKI progression with the receiver-operating characteristics (ROC) area under the curve (AUC) of 0.81 to 0.87. Measuring several biomarkers in addition to the furosemide stress test showed ROC AUC that was only slightly improved to 0.90 in predicting progression to stage III AKI [13]. There were no adverse effects. Given the predictive utility of the furosemide stress test in critically ill adults, there is reason to believe that a similar test would be useful in children.

Several factors play a role in AKI development in patients requiring cardiopulmonary bypass [14]. For patients who have postoperative AKI, the insult's timing is known [15]. Therefore, we undertook this study to determine whether early lack of furosemide responsiveness (LFR) after congenital heart surgery predicts AKI. We hypothesized that LFR after cardiopulmonary bypass surgery would predict AKI in a cohort of infants. In addition, we hypothesized that adjusting for surgical complexity would improve the diagnostic characteristics of LFR for AKI.

Patients and Methods

Inclusion Criteria

Infants (less than 1 year of age) who underwent congenital heart surgery from January 2013 to May 2015 at Children's Hospital of Philadelphia were reviewed. Patients on extracorporeal membrane oxygenation (n = 22), on renal replacement therapy (n = 2) immediately after surgery, and patients not requiring cardiopulmonary bypass were excluded (n = 108).

The standard furosemide dose was defined as 0.8 to 1.2 mg/kg, given 8 to 24 hours (median 12.8; interquartile range [IQR]: 9.8 to 18.2) after return from the operating room. The mean dose of furosemide received was 0.98 mg/kg (SD 0.06). Patients receiving nonstandard doses or continuous infusions of furosemide (n = 104) or additional diuretics between 2 and 6 hours after the initial furosemide dose (n = 60) were excluded. Continuous furosemide infusions have different pharmacokinetics compared with bolus dosing, which may limit the utility of LFR (details of the high-risk excluded patients are given in Supplement Tables 1 and 2).

Eleven excluded patients received early doses furosemide before 8 hours. These patients had a median age of 286 days (IQR: 224 to 345), median body surface area of 0.23 m^2 (IQR: 0.20 to 0.29 m^2), and median birth weight of 2.95 kg (IQR: 2.63 to 3.38 kg). Two of these patients received renal replacement therapy within 4 hours of surgery, and 3 required extracorporeal membranous oxygenation support. Of these 11 patients, 5 underwent a ventricular septal defect repair, 1 underwent pulmonary artery banding, 1 underwent atrial septal defect repair, 1 underwent arterial switch operation, 2 underwent hemi-Fontan procedure, and 1 had a Norwood operation.

This study was approved by the Institutional Board Review with waiver of informed consent.

Data Collection

Subject demographic data including age, sex, and body surface area were collected. Surgical complexity was determined using The Society of Thoracic Surgeons and the European Association for Cardiothoracic Surgery congenital heart surgery mortality classification (STAT categories) [16]. Cardiopulmonary bypass time, cross-clamp time, and deep hypothermic arrest time were also noted. Vasoactive-inotropic score was calculated for the first 48 hours after surgery [17] as follows: vasoactive-inotropic score = dopamine dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$) + dobutamine dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$) + 100 × epinephrine dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$) + 10 × milrinone dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$) + 10,000 × vasopressin dose (units $\cdot kg^{-1} \cdot min^{-1}$) + 100 × norepinephrine dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$). Lengths of hospital and intensive care unit stay as well as mortality at 30 days and at medium-term follow-up (2.5 years after cardiac surgery) were noted.

Postoperatively, all patients had a urinary catheter, and urine output was measured continuously per standard practice. Urine output response was assessed after the first dose of furosemide. Daily fluid balance and first-morning serum creatinine levels were collected from time of surgery through postoperative day 7. The KDIGO and neonatal KDIGO criteria were used to determine AKI using serum creatinine criteria as appropriate based on patient age [6, 7]. Reference creatinine was the lowest preoperative serum creatinine. In infants aged 120 days or less, AKI was assessed as a 0.3 mg/dL or greater creatinine increase. In patients aged more than 120 days, AKI was assessed as a 0.2 mg/dL or greater creatinine increase.

Statistical Analysis

Given the low incidence of AKI in our cohort (especially of stage 2 and stage 3 AKI) and the questionable clinical