

## ANESTHESIOLOGY

# Noninvasive Urine Oxygen Monitoring and the Risk of Acute Kidney Injury in Cardiac Surgery

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## EDITOR'S PERSPECTIVE

### What We Already Know about This Topic

- Cardiac surgery–associated acute kidney injury is associated with significant morbidity and mortality.
- A major contributor to acute kidney injury is renal hypoxia.
- Assessing for acute kidney injury using rise in serum creatinine often delays identification to 1 to 3 days after onset of acute kidney injury.
- There is a need to develop methods for real-time assessment for renal hypoxia, as this should allow for earlier interventions to prevent acute kidney injury.

### What This Article Tells Us That Is New

- This prospective single-center observational pilot study measured urinary oxygen partial pressure and urine flow in 91 patients undergoing cardiac surgery using a novel device placed between the urinary catheter and collecting bag. Urinary oxygen partial pressure was successfully measured in 86 of these patients.
- Mean urinary oxygen partial pressure in the period after cardiopulmonary bypass was significantly lower in patients who subsequently developed acute kidney injury than in those who did not.
- Future studies are needed to validate these findings at other centers.

Acute kidney injury (AKI) is a common complication of cardiac surgery with an incidence of 19 to 42%, and renal replacement therapy is required in 1 to 3% of

## ABSTRACT

**Background:** Acute kidney injury (AKI) is a common complication of cardiac surgery. An intraoperative monitor of kidney perfusion is needed to identify patients at risk for AKI. The authors created a noninvasive urinary oximeter that provides continuous measurements of urinary oxygen partial pressure and instantaneous urine flow. They hypothesized that intraoperative urinary oxygen partial pressure measurements are feasible with this prototype device and that low urinary oxygen partial pressure during cardiac surgery is associated with the subsequent development of AKI.

**Methods:** This was a prospective observational pilot study. Continuous urinary oxygen partial pressure and instantaneous urine flow were measured in 91 patients undergoing cardiac surgery using a novel device placed between the urinary catheter and collecting bag. Data were collected throughout the surgery and for 24 h postoperatively. Clinicians were blinded to the intraoperative urinary oxygen partial pressure and instantaneous flow data. Patients were then followed postoperatively, and the incidence of AKI was compared to urinary oxygen partial pressure measurements.

**Results:** Intraoperative urinary oxygen partial pressure measurements were feasible in 86/91 (95%) of patients. When urinary oxygen partial pressure data were filtered for valid urine flows greater than  $0.5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ , then 70/86 (81%) and 77/86 (90%) of patients in the cardiopulmonary bypass (CPB) and post-CPB periods, respectively, were included in the analysis. Mean urinary oxygen partial pressure in the post-CPB period was significantly lower in patients who subsequently developed AKI than in those who did not (mean difference, 6 mmHg; 95% CI, 0 to 11;  $P = 0.038$ ). In a multivariable analysis, mean urinary oxygen partial pressure during the post-CPB period remained an independent risk factor for AKI (relative risk, 0.82; 95% CI, 0.71 to 0.95;  $P = 0.009$  for every 10-mmHg increase in mean urinary oxygen partial pressure).

**Conclusions:** Low urinary oxygen partial pressures after CPB may be associated with the subsequent development of AKI after cardiac surgery.

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patients.<sup>1–5</sup> AKI after cardiac surgery has been associated with significant increases in mortality, intensive care unit (ICU) length of stay, and hospital costs.<sup>3,6</sup>

The Kidney Disease: Improving Global Outcomes clinical practice guidelines define AKI as an elevation in serum creatinine greater than 0.3 mg/dl above baseline or prolonged oliguria (greater than 6h).<sup>7</sup> Both of these criteria, however, take several hours to days to become diagnostic. It is this delay in diagnosis that has limited the development of effective mitigation strategies for cardiac surgery–associated AKI. More recently, serum and urinary biomarkers of renal injury have been developed for earlier detection of AKI.<sup>8–10</sup> While there is evidence to suggest that some of these

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biomarkers may predict AKI after cardiopulmonary bypass (CPB), bioassays can be performed only intermittently, require time for processing, and can be expensive. As such, a real-time intraoperative monitor for renal injury risk may be warranted.

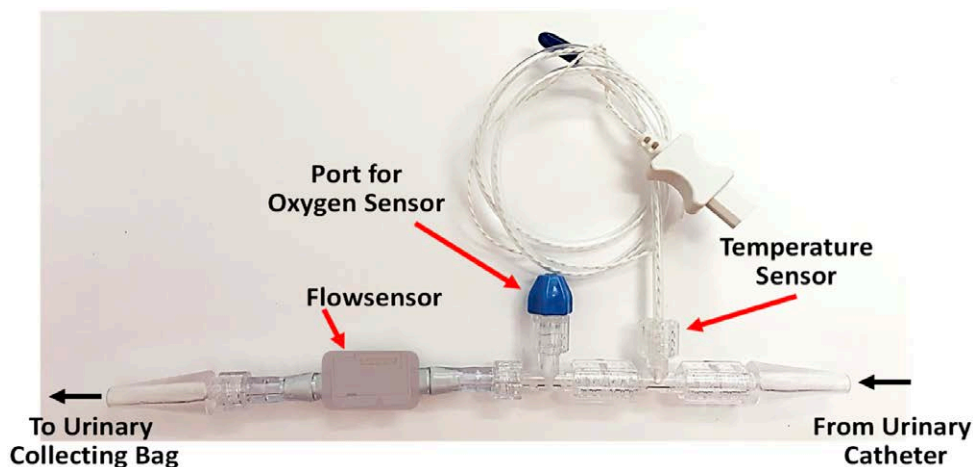
The pathophysiology of AKI after cardiac surgery is likely multifactorial, but decreased oxygen delivery and renal hypoxia are thought to be important factors.<sup>11,12</sup> The region of the kidney that is most susceptible to hypoxic injury is the renal medulla because of the high metabolic rate of the thick ascending limbs of renal tubules in that area and relatively low tissue perfusion compared with the renal cortex. The vasa recta are a network of postglomerular peritubular capillaries within the medulla that lie in close proximity to the urinary collecting ducts. Thus, when urine is first excreted, urinary oxygen partial pressure is similar to that of the renal medulla.<sup>13,14</sup> As such, continuous urinary oxygen partial pressure measurements might be used as a real-time monitor of renal hypoxia and injury risk. Urinary oxygen partial pressure in the bladder has been shown to decrease in the setting of sepsis, reduced renal blood flow, and decreased cardiac output.<sup>15,16</sup> In humans, urinary oxygen partial pressure measured either in the bladder or with a polarographic electrode placed in the urinary catheter has been shown to be predictive of postoperative AKI in cardiac surgery patients.<sup>17,18</sup> We have created a prototype investigational urinary oximeter that can be placed between the urinary catheter and collection bag to monitor continuous urinary oxygen partial pressure measurements (fig. 1). As urine passes through the device, urinary oxygen partial pressure, temperature, and instantaneous flow rate are measured. The novelty of our approach is that it is noninvasive (as opposed to within the bladder), provides continuous flow measurements that are used to determine the accuracy of urinary oxygen partial pressure measurements, is capable

of providing second-to-second data, and does not need to be continually calibrated. This was an observational pilot study to test the feasibility of intraoperative urinary oxygen partial pressure measurements using this novel device. We hypothesized that intraoperative urinary oxygen partial pressure measurements are feasible and that low urinary oxygen partial pressure is associated with AKI based on the Kidney Disease: Improving Global Outcomes criteria. Our secondary hypothesis was that low urinary oxygen partial pressure is associated with increased ventilator time, ICU length of stay, and hospital length of stay.

## Materials and Methods

This was a prospective observational study approved by the Institutional Review Board of the University of Utah (Salt Lake City, Utah) and was registered in ClinicalTrials.gov (NCT03335865). Patients were enrolled from February 2018 to November 2019. We enrolled a convenience sample of adult cardiac surgery patients undergoing procedures that required CPB and in whom a urinary catheter was placed during surgery. Eligible patients were screened 1 week ahead of time according to research staff and device availability. The patients during these weekly screenings who had the highest risk for postoperative AKI based on the Cleveland Risk Score were then approached for consent.<sup>19</sup> Exclusion criteria included preoperative end-stage kidney disease requiring dialysis, emergency surgery, preoperative extracorporeal membrane oxygenation, or patient refusal. When multiple surgeries occurred in a single patient, analysis was restricted to the first surgery.

After written informed consent, the patient was brought to the operating room, monitors were placed, and anesthesia was induced at the discretion of the attending anesthesiologist. Typically, a combination of midazolam, fentanyl,



**Fig. 1.** Urinary oximeter used in this study, including flow sensor, oxygen sensor port, and temperature sensor as well as the direction of urine flow from the urinary catheter, through the device, to the collecting bag.

propofol, and ketamine was used for induction with isoflurane and bolus fentanyl for maintenance of anesthesia. Patients received mannitol at the discretion of the attending anesthesiologist for volume management or to improve hematocrit on CPB. No other diuretic was used intraoperatively. After induction of anesthesia, the urinary oximeter was connected between the urinary catheter and the collecting bag, and then the urinary catheter was placed in a standard sterile fashion. In the operating room, the urinary oximeter was secured to the surgical bed to prevent kinking. Continuous urinary oxygen partial pressure and instantaneous flow rate were recorded from the patient for the entire operative period as well as postoperatively in the ICU for 24 h after the end of CPB.

Mean arterial pressure was continuously measured using either a radial or femoral arterial catheter. Continuous cardiac output monitoring *via* a pulmonary artery catheter was indexed to body surface area and recorded as cardiac index. Cerebral oximetry was measured intraoperatively using near-infrared spectroscopy. CPB was initiated after arterial and venous cannulation. Upon completion of the surgical procedure, patients were weaned from CPB. Epinephrine and milrinone infusions were used for inotropic support. Vasopressin and norepinephrine infusions were used as vasopressors. Arterial blood gases were obtained intraoperatively as determined by the anesthesia team and the perfusionist. After chest closure, patients were transferred to the ICU with either propofol or dexmedetomidine infusions for sedation as needed. In the ICU, urinary oxygen partial pressure and instantaneous flow rate were measured continuously until the device was removed (no later than 24 h after termination of CPB). All clinicians including the anesthesiologists, surgeons, perfusionists, intensivists, and ICU nursing staff caring for the patients were blinded to the continuous urinary oxygen partial pressure and instantaneous flow rate measurements. In the ICU, serum creatinine was measured upon admission and then at least daily along with other clinically indicated blood work. These data were collected until discharge from the ICU or postoperative day 7, whichever came first. Urine output was measured hourly by the nursing staff and recorded in the medical record until the urinary catheter was removed.

### Urinary Oximeter Calibration and Filtering

The device measured urinary oxygen partial pressure with an optical oxygen sensor that uses dynamic luminescence quenching (PreSens Precision Sensing GmbH, Germany). In this sensor, an indicator dye immobilized on a small polymer disc is interrogated *via* an optical fiber. The indicator dye's luminescence is highly specific to oxygen, and both its intensity and its luminescent decay time are affected by oxygen partial pressure through the Stern–Volmer relationship. It is necessary to correct the measurement for temperature, as luminescent intensity and decay time are temperature-dependent.<sup>20</sup> In contrast to polarographic

oxygen sensors, which rely on electrochemical principles to measure oxygen, optical luminescent sensors do not consume oxygen and can be operated without calibration over many days. In addition, the urinary oximeter contained a thermal-based flow sensor (Sensirion AG, Switzerland) and a standard temperature sensor. The resolution of the oxygen sensor ( $\pm 0.2$  to  $0.3$  mmHg) is within the range of oxygen partial pressure measurements obtained in this study.

Each sensor (oxygen partial pressure, flow, and temperature) provided data once a second (1 Hz). The flow and temperature data were directly sampled into a tablet computer. The luminescence measurements were made *via* optical fiber and stored, also once a second, in a dedicated device (PreSens Precision Sensing GmbH, Germany) from where it was later downloaded for processing and analysis.

With this novel urinary oximeter, each sensor was calibrated individually. Sensors were sterilized before use, and the effect of the sterilization process on sensor calibration is unknown. Sensors were therefore calibrated after removal from the patient, using a simulated urine solution. The optical signal and temperature were recorded at 0% and 13% oxygen concentrations at room and elevated temperatures. Using these data and multivariable linear regression, calibration constants were calculated for each sensor. Temperatures measured by the device and average calibration constants were then used in the calculation of urinary oxygen partial pressure from the luminescence measurements.

In addition to measuring the flow rate, the flow sensor detected and flagged two different conditions of measurement inaccuracy: (1) if there was air in line, or (2) if an excessive flow event occurred (defined as when the flow rate exceeded 1,000 ml/h, the upper limit of the optimal range of the flow sensor). Air and/or excessive flow events were very brief and often occurred immediately after urinary catheter placement or during patient position changes.

Data points that represented negative flow rate (back-flow) were flagged as invalid and triggered an algorithm that tracked the volume of negative flow. Then, when the flow moved in the positive direction again, the algorithm continued to flag data points as invalid until the urine that had flowed backwards was past the sensor. In the majority of patients, these errors represented less than 4% of the data.

Previous work in animals suggested that the accuracy of urinary oxygen partial pressure measurements made distal to the renal pelvis depends on urinary flow rate.<sup>21,22</sup> Because this novel urinary oximeter had not yet been tested in humans, we did not know the specific urinary flow rate below which our urinary oxygen measurements would become inaccurate. We chose to filter the oxygen data to measure only during urinary flows of greater than  $0.5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  as this is a widely accepted threshold for oliguria, and flows below this threshold should already identify the patient as at risk for AKI. After the data were filtered for low flow, if 30% or more of the data points were valid for a specific patient and time period (CPB or post-CPB), then

an average urinary oxygen partial pressure was calculated for that patient and time period. The mean and SDs of urinary oxygen partial pressure reported in the results section are group means and group SDs calculated from the average urinary oxygen partial pressure values of individual patients across the two time periods. The filtering criterion of  $0.5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  was decided on before the analysis, and no other thresholds were analyzed.

## Outcomes

The primary outcome measure for this study was the incidence of AKI as defined by the Kidney Disease: Improving Global Outcomes guidelines, specifically either an increase in serum creatinine by greater than  $0.3 \text{ mg/dl}$  from baseline within 48 h, an increase in serum creatinine greater than 1.5 times baseline within 7 days, or urine output less than  $0.5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  for more than 6 h within the first 48 h.<sup>7</sup> All of these time periods were measured beginning at ICU admission. Severe AKI was defined by the Kidney Disease: Improving Global Outcomes stages 2 or 3, specifically as an increase in serum creatinine greater than 2.0 to 2.9 times baseline (stage 2) or an increase in serum creatinine greater than 3.0 times baseline or greater than  $4 \text{ mg/dl}$ , or initiation of renal replacement therapy (stage 3).<sup>7</sup> A combined outcome of death or persistently elevated serum creatinine (greater than  $0.3 \text{ mg/dl}$  from baseline) at discharge was also determined. Other secondary outcome measures were ventilator time, ICU length of stay, and hospital length of stay.

## Statistical Analysis

As the relationship between urinary oxygen partial pressure measurements made with this novel device and the subsequent development of AKI had not been previously studied, we took an exploratory approach to the analysis. The data analysis and statistical plan were written after the data were accessed, and then additional analyses were done at the request of peer reviewers. This is the primary analysis of these data.

Patient characteristics were compared between AKI and non-AKI groups using either a two-sample chi-square test or Fisher exact test, as appropriate, for categorical variables. For continuous variables, we used an independent samples *t* test or Wilcoxon rank sum test, as appropriate. Histograms were used to identify skewed data. Data were presented as means with either SD or 95% CI when an independent samples *t* test was used or median with interquartile range when the Wilcoxon rank sum test was used. Pearson correlation was used to check for collinearity between urinary oxygen partial pressure and other variables. To compare serum creatinine between the AKI and non-AKI groups for the nine perioperative time points, we used independent sample *t* tests and Hommel's multiple comparison adjustment.<sup>23</sup> Two-tailed testing was used

for all comparisons. STATA version 15.1 (StataCorp LLC, USA) was used for the analysis.

The intraoperative period was divided into two time periods: CPB and post-CPB. The CPB period was from the start of the first CPB run to the end of the last CPB run if there were multiple periods of CPB. The post-CPB was the time period between the end of CPB and the end of surgery.

As there is currently no well-established cutoff for mean urinary oxygen partial pressure measured that distally in a urinary catheter, we used an exploratory approach to identify a meaningful cutoff for AKI. Receiver operating characteristic curve analysis was used to determine the range of cutoffs for urinary oxygen partial pressure that best predicted AKI using the Kidney Disease: Improving Global Outcomes criteria (creatinine or oliguria), AKI by creatinine only criteria, AKI by oliguria criteria, severe AKI by creatinine (Kidney Disease: Improving Global Outcomes stage 2/3 only), and a composite outcome of either death or persistently elevated serum creatinine at discharge (greater than  $0.3 \text{ mg/dl}$  increase from baseline).<sup>7</sup> Cutoff values were then varied by 1 mmHg until a single cutoff was identified that best predicted all outcomes. Risk ratios for the binary AKI outcome were estimated using a univariable binary Poisson regression model with a robust standard error.<sup>24</sup> Multivariable binary Poisson regression models with robust standard errors were created to control for potential confounders. Beginning with all perioperative variables with  $P < 0.20$  in the univariable analysis, variables were then eliminated in an interactive backward elimination fashion until all remaining variables had a  $P < 0.05$ . To assess the stability of the model, the bootstrap inclusion fraction was computed for each predictor variable.<sup>25,26</sup> Predictors with bootstrap inclusion fractions greater than 50%, indicating the variable remained significant in the final model in greater than 50% of the resamples, were determined to be reliable and not due to overfitting.

## Sample Size Calculation

An *a priori* sample size calculation was done using the means and SDs from a similar study measuring urinary oxygen partial pressure in the bladder during cardiac surgery.<sup>17</sup> Assuming an AKI incidence of 40%, 89 total patients were needed to detect a difference in the mean urinary oxygen partial pressure at a power of 80% using a two-sided significance level of 0.05. As this was the first time this urinary oximeter was to be used in the operating room, we did not know how feasible the measurements would be or how often the device would malfunction. We also only consented patients at least 1 day before surgery. We did not know ahead of time how often surgeries would be canceled or rescheduled. We therefore planned to enroll up to 200 patients in hopes of achieving successful monitoring in 100 patients.

## Results

### Feasibility of Urinary Oximeter Measurements

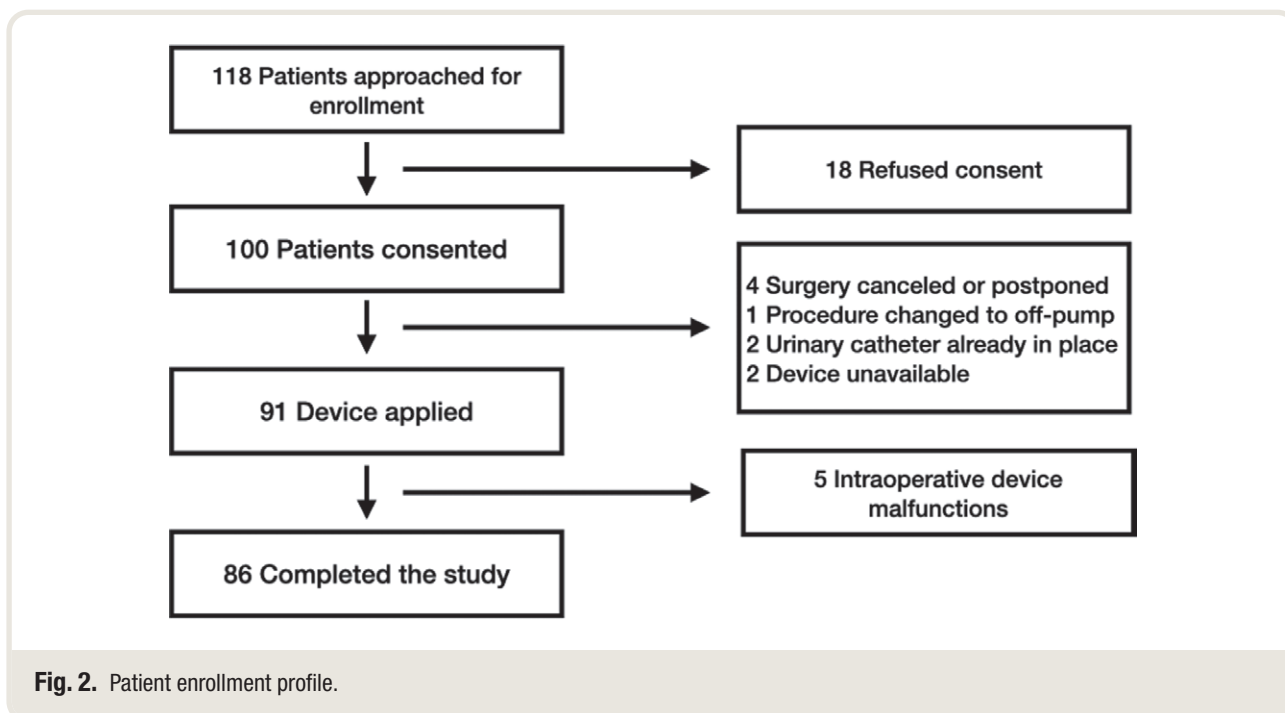
Figure 2 describes the study profile. Ninety-one patients had a urinary oximeter placed. In five of these patients, the device malfunctioned in the operating room, and they were excluded from the study. The first of these was the very first patient enrolled. In this patient, urine leaked from between the joints of the urinary oximeter. The study was halted, and we discovered that the sterilization process had caused the plastic of the device to shrink. After this, we sealed the joints with EP30Med biocompatible glue (Master Bond, USA), and the problem did not occur again. In three patients, the flow sensor malfunctioned or was not connected properly. Without flow data, the urinary oxygen partial pressure measurements could not be filtered for low flows. In one further patient, the oxygen sensor malfunctioned. This left 86 of 91 (95%) patients with intraoperative urinary oxygen partial pressure and urinary flow measurements.

In the CPB period, 70 of 86 (81%) patients (41/53 [77%] with AKI and 29 of 33 [88%] without) had valid urine flows greater than  $0.5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  for greater than 30% of the time period and were included in the analysis. The median (interquartile range) percentage of valid data for each patient analyzed in the CPB period was 75% (58 to 84). In the post-CPB period, 77 of 86 (90%) patients (47 of 53 [89%] with AKI and 30 of 33 [91%] without) had valid urine flows greater than  $0.5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  for greater than 30% of the time period and were included in the analysis. The median (interquartile range) percentage of

valid data for each patient analyzed in the post-CPB period was 78% (57 to 92). In the ICU period, only 32/86 (37%) patients (13 of 53 [25%] with AKI and 19/33 [58%] without) had valid urine flows greater than  $0.5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  for greater than 30% of the time period. The median (interquartile range) percentage of valid data for each patient analyzed in the post-CPB period was 40% (34 to 47). The ICU time period, therefore, was excluded from the urinary oxygen partial pressure analysis because there were too few patients with adequate urine flow to make a meaningful comparison.

### Incidence of AKI

Of the 86 patients who completed the study, 53 (62%) developed AKI. Twenty-one of those patients met AKI criteria by creatinine elevation only, and of these, 10 patients had severe AKI (Kidney Disease: Improving Global Outcomes stages 2/3). Five patients (5.9%) required renal replacement therapy. One patient died before discharge, and 10 patients had persistently elevated serum creatinine at discharge. Thirty-two patients met AKI criteria by oliguria only. Table 1 compares the preoperative clinical characteristics and risk factors of the patients who subsequently developed AKI (defined by Kidney Disease: Improving Global Outcomes criteria of creatinine elevation or oliguria) and those who did not. In univariable analyses, body mass index and preoperative insulin-dependent diabetes mellitus were associated with postoperative AKI. Table 2 compares the intraoperative hemodynamic and management data for patients who subsequently developed AKI and those who did not.



**Table 1.** Demographics and Preoperative Risk Factors

	No AKI (n = 33)	AKI (n = 53)	P Value
Age (yr), mean ± SD	62 ± 16	64 ± 12	0.628
Female, n (%)	10 (30)	18 (34)	0.725
Body mass index (kg/m <sup>2</sup> ), mean ± SD	26 ± 5	30 ± 6	0.006
Type of surgery			
Isolated CABG, n (%)	8 (24)	16 (30)	0.550
Single valve, n (%)	7 (21)	13 (25)	0.723
Single valve + CABG, n (%)	3 (9)	8 (15)	0.418
> 1 Valve, n (%)	4 (12)	6 (11)	0.910
Left ventricular assist device, n (%)	4 (12)	4 (8)	0.476
Other, n (%)*	8 (24)	8 (15)	0.289
Risk factors/comorbidities			
New York Heart Association Class > II, n (%)	10 (30)	18 (34)	0.725
Left ventricular ejection fraction < 35%, n (%)	3 (9)	7 (13)	0.562
Preoperative intra-aortic balloon pump, n (%)	0 (0)	1 (2)	> 0.999
COPD, n (%)	5 (15)	3 (6)	0.251
Insulin-dependent diabetes, n (%)	2 (6)	15 (28)	0.012
Redo sternotomy, n (%)	8 (24)	8 (15)	0.289
Baseline creatinine (mg/dl), mean ± SD	1.11 ± 0.51	1.14 ± 0.31	0.700
Glomerular filtration rate (ml · min <sup>-1</sup> · 1.73 m <sup>-2</sup> ), mean ± SD	75 ± 26	67 ± 20	0.109
Cleveland Risk Score, mean ± SD	4 ± 2	4 ± 2	0.867
Euroscore (%), median (interquartile range)	3 (2–7)	3 (2–5)	0.461

The diagnosis of acute kidney injury (AKI) was based on the Kidney Disease: Improving Global Outcomes criteria.<sup>7</sup> Categorical variables compared with chi-square test or Fisher exact test and continuous variables compared with an independent sample *t* test or Wilcoxon rank sum test. There were no missing data in this table.

\*Other, septal myectomy, aortic procedures, and pulmonary endarterectomies.

CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease.

## Urinary Oxygen Data

Figure 3 provides an example of the intraoperative record of a 50-yr-old male patient who subsequently developed AKI. This patient had a period of significant hypoxemia and hypotension immediately after weaning from CPB that only resolved after initiating inhaled pulmonary vasodilators. During this period, there was also a decrease in both cerebral oximetry and urinary oxygen partial pressure.

For the 70 patients analyzed in the CPB period, the range of individual mean urinary oxygen partial pressure values was 18 to 66 mmHg, and the group mean ± SD was 38 ± 11 mmHg. The coefficient of variation was 0.29. During this time period, there was no difference in mean urinary oxygen partial pressure between patients who subsequently developed AKI and those who did not (mean difference, 1 mmHg; 95% CI, -4 to 7; *P* = 0.613). For the 77 patients analyzed in the post-CPB period, the range of individual mean urinary oxygen partial pressure values was 10 to 74 mmHg, and the group mean ± SD was 39 ± 12 mmHg. The coefficient of variation was 0.31. During this time period, however, mean urinary oxygen partial pressure was lower in those patients who subsequently developed AKI compared to those who did not (mean difference, 6 mmHg; 95% CI, 0 to 11; *P* = 0.038). When multivariable analysis was done to adjust for confounders, mean urinary oxygen partial pressure in the post-CPB remained significantly associated with AKI. For every 10-mmHg increase

in post-CPB mean urinary oxygen partial pressure, there was a 18% reduction in the risk of AKI (relative risk, 0.82; 95% CI, 0.71 to 0.95; *P* = 0.009). We did not identify any collinearity in this model (all *r* values less than 0.15 and all *P* values greater than 0.17). Figure 4 shows the timing of urinary oxygen partial pressure changes compared to that of serum creatinine elevation over a 7-day time period. Mean urinary oxygen partial pressure was significantly lower in AKI patients during the operative period (post-CPB), while serum creatinine did not become significantly elevated until postoperative day 2.

Table 3 shows a sensitivity analysis comparing post-CPB urinary oxygen partial pressure to various definitions of AKI. Mean urinary oxygen partial pressure during the post-CPB period was associated with the primary definition of AKI (full Kidney Disease: Improving Global Outcomes criteria: creatinine or oliguria), but was not associated with oliguria alone, elevated creatinine alone, or severe AKI (stage 2/3). Using a threshold approach, however, a cutoff of mean urinary oxygen partial pressure less than 25 mmHg during the post-CPB period was found to be associated with the primary outcome of AKI (full Kidney Disease: Improving Global Outcomes criteria: creatinine or oliguria) as well as AKI by creatinine only, severe AKI, and death or persistently elevated creatinine at hospital discharge. These findings remained significant after multivariable analysis was used to adjust for confounders (full Kidney Disease: Improving Global Outcomes criteria: relative risk, 1.9; 95%

**Table 2.** Intraoperative Hemodynamic Variables and Risk Factors

	No AKI (n = 33)	AKI (n = 53)	Mean Difference (95% CI)	P Value*
Mean urine oxygen (mmHg), mean ± SD				
CPB	39 ± 12 n = 4 (12%) missing	38 ± 11 n = 12 (23%) missing	1 (−4 to 7)	0.613
Post-CPB	43 ± 13 n = 3 (9%) missing	37 ± 11 n = 6 (11%) missing	6 (0 to 11)	0.038
Mean urine flow (ml/kg/hr), mean ± SD				
CPB	2.1 ± 1.3	2.1 ± 1.7	0 (−0.7 to 0.6)	0.894
Post-CPB	1.8 ± 0.9	1.5 ± 1.3	0.3 (−0.3 to 0.8)	0.329
Mean arterial pressure (mmHg), mean ± SD				
CPB	67 ± 7 n = 0 missing	68 ± 8 n = 1 (2%) missing	−1 (−5 to 2)	0.386
Post-CPB	68 ± 5 n = 0 missing	68 ± 7 n = 1 (2%) missing	0 (−3 to 3)	0.917
Cerebral oximetry (%), mean ± SD				
CPB	69 ± 4 n = 8 (24%) missing	71 ± 7 n = 15 (28%) missing	−2 (−5 to 1)	0.295
Post-CPB	72 ± 6 n = 8 (24%) missing	71 ± 7 n = 15 (28%) missing	1 (−2 to 4)	0.586
Cardiac index (l · min <sup>−1</sup> · m <sup>−2</sup> ), mean ± SD				
CPB	2.2 ± 0.3 n = 1 (3%) missing	2.3 ± 0.2 n = 1 (2%) missing	0 (−0.2 to 0.1)	0.440
Post-CPB	2.6 ± 0.4 n = 16 (48%) missing	2.4 ± 0.4 n = 39 (74%) missing	0.2 (−0.1 to 0.5)	0.146
Minimum hemoglobin (g/dl), mean ± SD				
CPB	8.8 ± 1.6	8.4 ± 1.8	0.4 (−0.4 to 1.2)	0.300
Post-CPB	9.7 ± 1.5	9.3 ± 1.5	0.3 (−0.4 to 1.0)	0.359
Given mannitol, n (%)	26 (79)	33 (62)	17 (−3 to 36)	0.108
Crystalloid (l), mean ± SD	2.1 ± 0.8 n = 2 (6%) missing	2.0 ± 0.9 n = 1 (2%) missing	0.1 (−0.3 to 0.5)	0.559
Received erythrocyte transfusion, n (%)	12 (36)	19 (36)	0 (−20 to 21)	0.961
Received fresh frozen plasma transfusion, n (%)	11 (33)	24 (45)	−12 (−33 to 9)	0.273
Received platelet transfusion, n (%)	10 (30)	14 (26)	3 (−16 to 24)	0.696
CPB time (min), mean ± SD	167 ± 70	167 ± 70	0 (−31 to 31)	0.980

The diagnosis of acute kidney injury (AKI) was based on the Kidney Disease: Improving Global Outcomes criteria.<sup>7</sup> The mean and SD of urinary oxygen partial pressure reported in the results section are group means and group SDs calculated from the average urinary oxygen partial pressure values of individual patients during each time period.

\*Comparisons were made using either a two-sample chi-square test or Fisher exact test, as appropriate for categorical variables, and an independent samples *t* test or Wilcoxon rank sum test as appropriate for continuous variables.

CPB, cardiopulmonary bypass.

CI, 1.3 to 2.8; *P* = 0.001; creatinine elevation only: relative risk, 3.1; 95% CI, 1.4 to 6.9; *P* = 0.006; severe AKI: relative risk, 4.6; 95% CI, 1.4 to 15.3; *P* = 0.014; death or elevated serum creatinine at discharge: relative risk, 6.6; 95% CI, 1.6 to 27.6; *P* = 0.009). We did not identify any collinearity in these models (all *r* values less than 0.17 and all *P* values greater than 0.12).

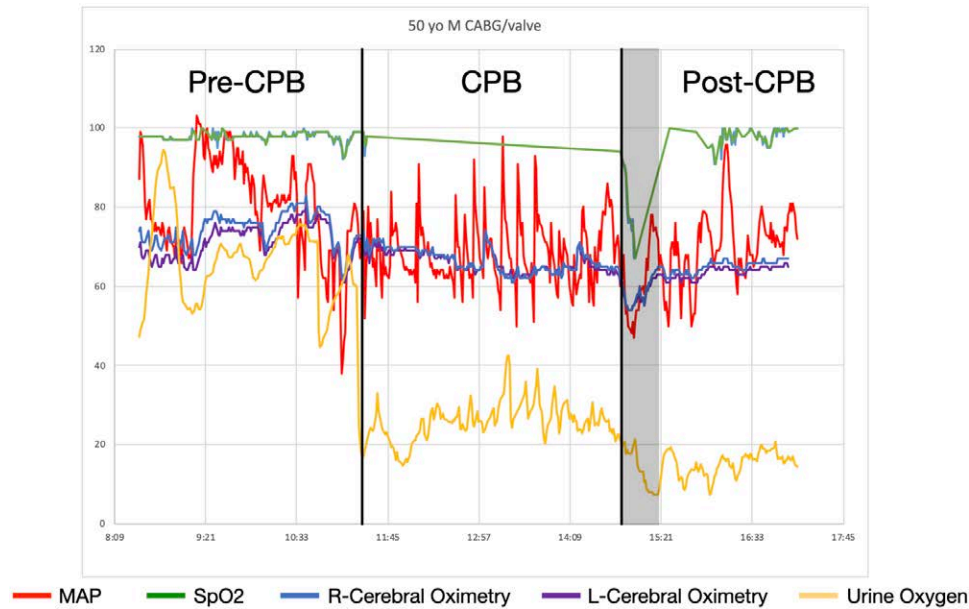
### Continuous Urinary Flow

Mean continuous urine flow (instantaneous flow rate) in the CPB and post-CPB was also compared to the primary outcome of AKI (full Kidney Disease: Improving Global Outcomes criteria: creatinine or oliguria) but did not differ between groups (table 2). Only 8 of 86 patients (9.3%) during the CPB period and 9 of 86 patients (10.5%) during the post-CPB period had a mean instantaneous flow

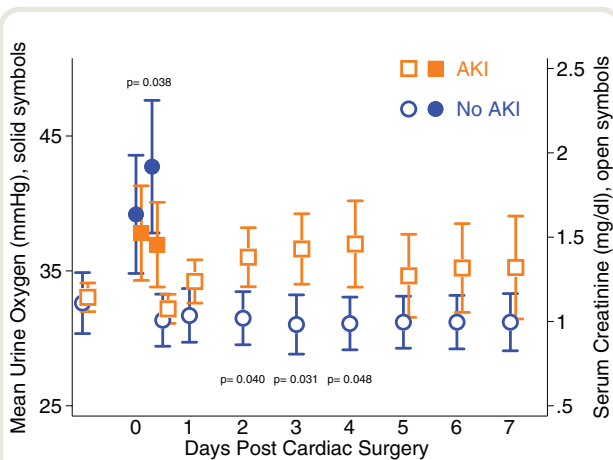
rate less than 0.5 ml · kg<sup>−1</sup> · h<sup>−1</sup>. There was no collinearity between urinary oxygen partial pressure and instantaneous flow rate during either the CPB (*r* = −0.066; *P* = 0.589) or post-CPB (*r* = 0.056; *P* = 0.627) periods.

### Mannitol

Mannitol administration was not associated with a significant difference in mean instantaneous flow rate during either time period (instantaneous flow rate for no mannitol *vs.* mannitol given during CPB: 1.9 *vs.* 2.2 ml · kg<sup>−1</sup> · h<sup>−1</sup>; *P* = 0.292; post-CPB: 1.7 *vs.* 1.5 ml · kg<sup>−1</sup> · h<sup>−1</sup>; *P* = 0.548). Mannitol administration was also not associated with a significant difference in urinary oxygen partial pressure during either time period (urinary oxygen partial pressure for no mannitol *vs.* mannitol given during CPB: 41 *vs.* 37 mmHg; *P* = 0.290; post-CPB: 39 *vs.* 39 mmHg; *P* = 0.949).



**Fig. 3.** An example of the intraoperative urinary oxygen partial pressure, mean arterial pressure (MAP), oxygen saturation measured by pulse oximetry ( $SpO_2$ ), and cerebral oximetry tracings from a patient who subsequently developed acute kidney injury. The *black lines* indicate the start and end of cardiopulmonary bypass (CPB). The *gray box* highlights a time period of both hypotension and hypoxemia after bypass. During this period, there was also a decrease in both cerebral oximetry and urine oxygen. MAP, *red*;  $SpO_2$ , *green*; right cerebral oximetry, *blue*; left cerebral oximetry, *purple*; urine oxygen partial pressure, *yellow*. CABG, coronary artery bypass graft.



**Fig. 4.** *Left axis:* The mean urinary oxygen partial pressure with 95% CI during the two intraoperative time periods (cardiopulmonary bypass and after cardiopulmonary bypass) for the patients who developed acute kidney injury (AKI; *orange solid squares*) and those who did not (*blue solid circles*). *Right axis:* Daily serum creatinine measurements with 95% CI from baseline until postoperative day 7 for patients who developed AKI (*orange open squares*) and those who did not (*blue open circles*). *P* values from comparisons at specific time points for the AKI and non-AKI groups are reported if less than 0.05. *P* values for serum creatinine were adjusted for multiple comparisons using Hommel's procedure.

### Other Secondary Outcomes

The median ventilator time was 14 (interquartile range, 10 to 30) h. Patients in the upper 25% of ventilator time had a significantly lower mean urinary oxygen partial pressure in the post-CPB period (mean difference, 7 mmHg; 95% CI, 1 to 13;  $P = 0.026$ ). Median ICU and hospital length of stay were 4 (interquartile range, 3 to 7) days and 9 (interquartile range, 7 to 13) days, respectively. There was no difference in mean urinary oxygen partial pressure for patients in the upper 25% of either ICU or hospital length of stay (mean difference, 1 and 0 mmHg;  $P = 0.807$  and  $P = 0.954$ , respectively).

### Discussion

Urine oxygen partial pressure has been called “a clinical window on the health of the renal medulla” as numerous studies have demonstrated a strong association with medullary oxygen concentrations.<sup>14</sup> In animal models, urinary oxygen partial pressure is a sensitive indicator of decreased renal blood flow.<sup>15,27</sup> In an ovine model of sepsis, restoration of mean arterial pressure with norepinephrine improved urine output but resulted in a further reduction of medullary oxygenation and urinary oxygen partial pressure.<sup>16</sup> Kainuma *et al.* found that cardiac surgery patients with decreased urinary oxygen partial pressure after CPB had significantly higher postoperative serum creatinine



**Table 3.** Sensitivity Analysis of Post-CPB Mean Urinary Oxygen Partial Pressure Compared to Various Definitions of AKI in 86 Patients

	No. (%) of Patients with AKI	Unadjusted Relative Risk of AKI for Every 10-mmHg Increase in Mean Urinary Oxygen Partial Pressure (95% CI)	P Value	Unadjusted Relative Risk of AKI if Mean Urinary Oxygen Partial Pressure < 25 mmHg (95% CI)	P Value
Full Kidney Disease: Improving Global Outcomes	53 (62)	0.84 (0.73–0.99)	0.032	1.51 (1.08–2.10)	0.015
Oliguria only	49 (57)	0.89 (0.76–1.04)	0.149	1.08 (0.61–1.92)	0.798
Creatinine only	21 (24)	0.92 (0.65–1.31)	0.650	2.46 (1.06–5.7)	0.036
Kidney Disease: Improving Global Outcomes Stage 2/3	10 (12)	0.70 (0.43–1.13)	0.147	3.70 (1.18–11.6)	0.025
Death or kidney injury at discharge	11 (13)	0.81 (0.50–1.31)	0.390	3.23 (1.06–9.9)	0.039

Comparisons were made using univariable binary Poisson regression with a robust standard error. During the period after cardiopulmonary bypass, there were nine patients who were excluded because of inadequate urinary oxygen partial pressure data after filtering for low or invalid urine flows. Full Kidney Disease: Improving Global Outcomes is creatinine elevation or oliguria based on the Kidney Disease: Improving Global Outcomes guidelines.

AKI, acute kidney injury; CPB, cardiopulmonary bypass.

concentrations.<sup>18</sup> More recently, Zhu *et al.* found that cardiac surgery patients who developed AKI had lower intraoperative urinary oxygen partial pressure.<sup>17</sup> We found that intraoperative urinary oxygen partial pressure measurements made with a noninvasive urinary oximeter placed distal to the urinary catheter were feasible, and a lower mean urinary oxygen partial pressure during the post-CPB period was independently associated with AKI.

Like Kainuma *et al.*, our urinary oxygen partial pressure measurements were taken from the urinary catheter, but we used luminescence quenching instead of a polarographic electrode, as the latter technology requires more frequent calibration. Zhu *et al.* also used luminescence, but their measurements were made within the bladder. In addition, we concomitantly measured urine flow and filtered for low flows, something that was not reported in either of the previous studies. The mean urinary oxygen partial pressure values we obtained during post-CPB (37 to 43 mmHg) were lower than the values found by Kainuma *et al.* (65 to 73 mmHg) but higher than those found by Zhu *et al.* (19 to 27 mmHg). It is possible that measuring urinary oxygen partial pressure distal to the bladder results in higher values because of the inadvertent ingress of oxygen into the urinary catheter from the surrounding tissue or atmosphere. Such oxygen ingress would be more pronounced during periods of low urine flow, which is why we took care to invalidate oxygen measurements when urine flows were very low. Kainuma *et al.* did not report this type of filtering, and that may explain why their oxygen partial pressure values were higher than ours. The oxygen permeability of urinary catheters and the subsequent effect on urinary oxygen partial pressure measurements need further evaluation.

Interestingly, both Kainuma *et al.* and Zhu *et al.* found that urinary oxygen partial pressure during the post-CPB period was associated with AKI, but urinary oxygen partial pressure during CPB was not. This is consistent with our findings and may be related to the difference in hemodynamic conditions that occur during CPB *versus*

immediately after weaning. Recent work suggests that renal oxygen delivery decreases and oxygen extraction increases during CPB and that this impairment of renal oxygen supply/demand is even more pronounced in the post-CPB period.<sup>28</sup> During this time, low cardiac index, hemodilution, and the use of vasoactive agents contribute to poor oxygen delivery, while warm temperatures result in increased oxygen consumption. Thus, more renal hypoxia may occur in the post-CPB period than during CPB when the patient is cool and mechanically supported by the heart and lung machine.

The Kidney Disease: Improving Global Outcomes guidelines recommend using serum creatinine elevation and oliguria for the diagnosis of AKI. Both are reflections of glomerular filtration rate, a widely accepted index of renal function.<sup>7</sup> Accurate postoperative urine output data, however, are difficult to obtain, and many studies of cardiac surgery-associated AKI report only serum creatinine changes.<sup>17,29–31</sup> Other investigators may forgo urine output criteria for AKI because of the use of diuretics such as mannitol or because of acute shifts in fluid balance that occur in the perioperative period. The prognostic value of oliguria after cardiac surgery is uncertain.<sup>32–34</sup> Creatinine criteria appear to be more closely associated with ICU length of stay and short-term mortality, whereas urine output criteria may be more associated with long-term mortality.<sup>32,33</sup>

The severity of AKI after cardiac surgery is known to have a proportional effect on mortality and hospital costs.<sup>3,6,35</sup> In one study, severe AKI accounted for up to 94% of hospital costs, 10 times the mortality compared to those without AKI, and 5 times the mortality compared to those with mild AKI.<sup>6</sup> We found that mean urinary oxygen partial pressure was associated with severe AKI (Kidney Disease: Improving Global Outcomes stage 2/3) if a threshold approach was used with a cutoff of 25 mmHg. These results need further validation in larger studies where severe AKI is the primary outcome.

Decreased urinary flow during CPB has previously been described as a risk factor for AKI, although CPB urinary flows appear to be higher than during other perioperative periods.<sup>36,37</sup> Hori *et al.* found that the optimal cutoff to predict postoperative AKI was a urine output of less than  $1.5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  during CPB and that only 5.7% of patients had CPB urine output less than  $0.5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  when 30% of patients developed AKI.<sup>37</sup> Similarly, we found that only 9.3% of patients during CPB had a mean instantaneous flow rate less than  $0.5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ , while 63% of our patients developed AKI. These findings suggest that this well-described cutoff for oliguria may not be useful during CPB.

There is conflicting evidence about the effect of mannitol on cardiac surgery-associated AKI.<sup>38–40</sup> Although generally used as an osmotic diuretic, we found that the administration of mannitol did not have a statistically significant effect on instantaneous flow rate. This might have been because of relatively low doses used or because urinary flows after the initiation of CPB are already generally high, blunting the effect of mannitol administration. Previous studies have suggested that urinary oxygen partial pressure measurements may be affected by the use of diuretics such as furosemide.<sup>41</sup> In our study, however, mannitol had no significant effect on urinary oxygen partial pressure during either time period.

## Limitations

The first limitation of this study was the exploratory approach taken in the analysis. This was the first time the device was tested either in humans or in animals. No established threshold exists for urinary oxygen partial pressure, and this small pilot study was not powered for diagnostic validation. We theorized that the relationship between urinary oxygen partial pressure and the subsequent development of AKI might be more of a threshold response than a linear dose response. Indeed, a mean urinary oxygen partial pressure less than 25 mmHg during the post-CPB period was associated with AKI as defined by the full Kidney Disease: Improving Global Outcomes criteria as well as creatinine elevation alone, severe AKI, and a combined outcome of death or persistently elevated creatinine at discharge. The cutoff of 25 mmHg was discovered in an exploratory fashion, however, and should not be adopted for clinical use without proper validation.<sup>42,43</sup>

The second limitation was a technical limitation in the accuracy of urinary oxygen partial pressure in stagnant urine. During low flow, urine in the catheter could be subject to the ingress of oxygen from the surrounding tissue or environment and may poorly reflect the concurrent oxygen environment of the medulla.<sup>21</sup> Indeed, we observed that very low flow or no flow states were associated with elevated urinary oxygen partial pressure measurements. To account for this limitation, we filtered out urinary oxygen partial pressure data during periods of low flow. Because

this noninvasive urinary oximeter is so new, we did not know the precise flow below which urinary oxygen partial pressure measurements would become inaccurate. We therefore used a clinically relevant flow for filtering ( $0.5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ). We reasoned that flows below this rate would be considered at risk for AKI regardless of the urinary oxygen partial pressure. We also arbitrarily chose to include patients from each time period if greater than 30% of their urinary oxygen partial pressure data were valid after filtering for these low flows. The actual percentage of valid data, however, was much higher in the majority of patients. Filtering may have limited the feasibility of the device as patients with persistently low urine flows were excluded. This could have led to selection bias. No other filtering criteria were evaluated. Future work should be directed at determining the flow below which urinary oxygen partial pressure measurements become inaccurate when using this noninvasive urinary oximeter. This could be done through mathematical modeling, *in vitro* studies, or animal models.

Another limitation is that we did not record diuretic use in the ICU. Although rarely used in our ICU in the first 24 h postoperatively, diuretic use may have confounded our definition of AKI. Finally, although this was a convenience sample, we enrolled patients at high risk for AKI to ensure an adequate incidence of the primary outcome. This could also have contributed to selection bias. Future work should focus on high- and low-risk patients.

## Conclusions

Intraoperative measurements of urinary oxygen partial pressure are feasible using a noninvasive device placed distal to the urinary catheter. Urinary oxygen partial pressure in the post-CPB period was associated with AKI after cardiac surgery. Further research is needed to validate these findings and to elucidate whether urinary oxygen partial pressure can be used to trigger interventions to successfully prevent or reduce the severity of cardiac surgery-associated AKI.

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### Competing Interests

Dr. Silverton, Dr. Kuck, B. Stringer, S. Shumway, and L. Lofgren are inventors on a patent application for the urine oxygen and flow sensing technology. This prototype is under development for commercial consideration by Dr. Silverton, Dr. Kuck, B. Stringer, and S. Shumway, but as of yet, no commercial activity has occurred. The other authors declare no competing interests. This work was performed under a conflict of interest management plan approved by the University of Utah Conflict of Interest Office (Salt Lake City, Utah). This included disclosure of conflict of interest to patients and collaborators and an independent peer review of the data analysis. The interpretation and reporting of these data are the responsibility of the authors alone and should not be seen as an official policy of or interpretation by the U.S. Government, nor does this report necessarily represent the official views of the National Institutes of Health (Bethesda, Maryland).

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