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A Decline in intraoperative Renal Near Infrared Spectroscopy is associated with Adverse Outcomes in Children following Cardiac Surgery

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Abstract

Objective—Renal near infrared spectroscopy (NIRS) is known to be predictive of acute kidney injury (AKI) in children following cardiac surgery using a series of complex equations and area under the curve. This study was performed to determine if a 20% reduction in renal NIRS for 20 consecutive minutes intra-operatively or within the first 24 post-operative hours is associated with 1) AKI, 2) increased AKI biomarkers, or 3) other adverse clinical outcomes in children following cardiac surgery.

Design—Prospective single center observational study

Setting—Pediatric cardiac intensive care unit

Patients—Children less than or equal to age 4 years who underwent cardiac surgery with the use of cardiopulmonary bypass during the study period (June 2011 to July 2012).

Interventions—None

Measurements and Main Results—A reduction in NIRS was not associated with AKI. 9/12 (75%) of patients with a reduction in renal NIRS did not develop AKI. The remaining 3 patients had mild AKI (pRIFLE-R). A reduction in renal NIRS was associated with the following adverse clinical outcomes: 1) a longer duration of mechanical ventilation ($p = 0.05$), 2) longer intensive care length of stay ($p = 0.05$), and 3) longer hospital length of stay ($p < 0.01$). A decline in renal NIRS in combination with an increase in serum IL-6 and serum IL-8 was associated with a longer intensive care length of stay, and the addition of urine IL-18 to this was associated with a longer hospital length of stay.

Conclusions—In this cohort, the rate of AKI was much lower than anticipated thereby limiting the evaluation of a reduction in renal NIRS as a predictor of AKI. A 20% reduction in renal NIRS was significantly associated with adverse outcomes in children following cardiac surgery. The addition of specific biomarkers to the model was predictive of worse outcomes in these patients. Thus, real time evaluation of renal NIRS using the specific levels of change of a 20% reduction for 20 minutes may be useful in predicting prolonged mechanical ventilation and other adverse outcomes in children undergoing cardiac surgery.

Introduction

Congenital heart disease is common, occurring in 4 out of every thousand live births [1]. It continues to be the most common congenital anomaly. Outcomes following repair of congenital heart defects have improved significantly over the past 2 decades. Nevertheless, these interventions are still fraught with significant morbidity. Acute kidney injury (AKI) affects 40% of children following cardiac surgery, and is associated with increased morbidity and mortality, including a longer duration of mechanical ventilation, and a longer intensive care unit and hospital length of stay [2–7]. The mechanisms for the development of AKI following cardiac surgery are many, including, but not limited to ischemia/reperfusion injury, oxidative stress, coagulopathy, micro-embolism and hypothermia [8, 9]. In children,

risk factors for the development of AKI include younger age at surgery, chromosomal abnormalities, younger gestational age at surgery, longer duration of cardiopulmonary bypass (CPB), increased surgical complexity, reduced preoperative renal function, preoperative need for mechanical ventilation and need for deep hypothermic circulatory arrest [10].

No effective strategies currently exist to prevent or treat AKI, and reliance on serum creatinine as a functional marker of this entity is hampered by the fact that it is a late marker of AKI, rising 24–72 hours after injury has occurred [11]. Many therapeutic trials in AKI have failed, partly due to the late diagnosis and lack of recognized successful interventions. Thus, identification of methods to detect AKI early is considered a research priority [11]. Recent progress in AKI research has led to the discovery of novel biomarkers that may allow for early detection of AKI, however, clinical scenarios in which to perform biomarker testing are yet to be defined.

Near infrared spectroscopy (NIRS) is a noninvasive tool that provides a continuous estimate of regional tissue oxygen saturation. The technology utilizes oxyhemoglobin and deoxy-hemoglobin to provide an estimate of regional tissue oxygen saturation (rSO₂) [12]. A reduction in NIRS over the organ in which it is placed is associated with hypo-perfusion and tissue ischemia, stemming from the fact that NIRS measurements are considered to utilize the Fick principle of oxygen supply and demand. Because cerebral NIRS has been correlated with jugular venous bulb oximetry, or “mixed venous saturation,” it serves as a surrogate for oxygen consumption. It has been demonstrated that in experimental shock states, use of cerebral NIRS as a hemodynamic target improved outcomes [13, 14]. Although some studies report a cerebral NIRS value of 50% or less as being predictive of worse outcomes, guidelines for what is considered to be a clinically relevant decline in cerebral or renal NIRS have not yet been established, especially in children with cyanotic congenital heart disease [15, 16]. Much of the literature has focused on the study of cerebral NIRS. The average of cerebral and renal NIRS has been described as approximately 78% and 87%, respectively, in normal, non-cyanotic and awake neonates over the first five days of life [17]. Thresholds and intervention strategies based on cerebral NIRS that improve outcomes are only partially validated, but in general, a cerebral NIRS value in the acyanotic patient of less than 60% will prompt further evaluation [18]. In our ICU, we have generally used a decline in the overall trend rather than absolute value for cerebral NIRS to consider further clinical evaluation in the cyanotic patients. This is similar for renal NIRS as the threshold for what is a meaningful decline in renal NIRS has yet to be determined.

Renal NIRS has been shown to be predictive of AKI in several small studies, using a series of complex equations or area under the curve (AUC) that do not have clinical relevance for predicting early AKI [19, 20]. One study reported a low renal oximetry of less than 50% for greater than 2 hours to be associated with AKI, and is the most clinically useful renal NIRS parameter assessed to date [21]. Many factors, including patient size, kidney depth, amount of subcutaneous fat, and use of certain medications, including methylene blue, may impact accuracy of renal NIRS monitoring [22].

The primary purpose of this study was to determine whether a change in renal NIRS of 20% reduction for 20 minutes during, or in the first 24 hours after cardiac surgery in children was associated with the following 1) AKI, 2) increased AKI biomarkers, 3) other adverse clinical outcomes.

Materials and Methods

Design

This was a single center prospective observational study conducted from June 2011 to July 2012 in the cardiovascular operating room and cardiac intensive care unit at Children's Hospital Colorado. The total duration of enrollment was 24 hours following the initiation of cardiopulmonary bypass. Inclusion criteria were all children less than or equal to age four years or 15kg undergoing either corrective or palliative congenital heart surgery or heart transplantation with cardiopulmonary bypass. The rationale for limiting the study population to 4 years of age and 15kg is that previously published literature that showed a good correlation between renal NIRS, renal vein and inferior vena cava saturation [22]. Exclusion criteria were all patients with AKI prior to surgery (defined as an abnormal calculated creatinine clearance using the pediatric Schwartz calculation for age [23], use of nephrotoxic drugs prior to surgery, significant renal abnormalities, or use of extracorporeal life support prior to, or during enrollment. Written informed consent was obtained from the parent or legal guardian prior to enrollment in the study. The institutional review board and ethics committee approved the study protocol.

The Predictor—We dichotomized patients into 2 groups based on: 1) patients with a than 20% reduction from baseline for 20 consecutive minutes (a “NIRS event”) during cardiac surgery or the first 24 hours after initiation of cardiopulmonary bypass and 2) patients without a 20% reduction in renal NIRS for 20 minutes. The percent reduction and duration were chosen based on our prior observations in the overall trend of renal NIRS monitoring that would alert the clinician to evaluate the patient. Over time, this had been our indicator without any prior knowledge of outcomes with this specific cut-off and duration. An INVOS™ 5100C Cerebral/Somatic Oximeter (Covidien, Boulder CO) was used to monitor cerebral and renal oximetry. A probe emits 2 different wavelengths of near-infrared light at 730 and 810nm, which correspond to spectral absorptions of oxygenated and deoxygenated blood. A qualified vascular ultrasonographer performed bedside renal ultrasound in order to determine the location of the left kidney, depth of the kidney from the skin, as well as maximal depth. The area was then marked for subsequent sensor placement in the operating room prior to anesthesia induction. The renal sensor was always placed on the left kidney, unless it was absent (1 patient). Renal NIRS monitoring was recorded at 33-second intervals from just prior to anesthesia induction until 24 hours after the initiation of cardiopulmonary bypass. Baseline renal NIRS was determined as the average value for the first 10 minutes of recording prior to the initiation of cardiopulmonary bypass when the patient was considered to be in “steady state.”

Outcomes—The primary outcome was AKI on post-operative day 1–3. AKI was defined using the pediatric RIFLE criteria [2]. Secondary outcomes were 1) an increase in AKI

biomarkers or 2) other adverse clinical outcomes. Electrolyte and serum creatinine measurements were performed at baseline, and then daily for the first 3 post-operative days. AKI was defined as the peak serum creatinine during the first three post-operative days (not including post-operative day 0), and stratified according to the pRIFLE criteria [2]. Risk (pRIFLE-R) is defined as a 25% increase in measured serum creatinine and injury (pRIFLE-I) is defined as a 50% increase in measured serum creatinine. Urinary AKI biomarkers including urine interleukin-18 (IL-18), urine neutrophil gelatinase associated lipocalin (NGAL), urine interleukin-6 (IL-6), serum interleukin-8 (IL-8) and serum IL-6 were assessed at baseline and then at 2, 6, 12 and 24 hours after the initiation of cardiopulmonary bypass.

Urine IL-18 and urine NGAL have been extensively studied as potential early biomarkers of AKI in general, and after bypass requiring surgery in children in particular. Specifically, increased levels of urine IL-18 or urine NGAL by 6 hours post procedure has been shown to predict AKI after cardiac bypass surgery in children with areas under the curve of 0.72 and 0.71, respectively [24]. The rise in urine IL-18 and NGAL is thought to occur due to renal tubular injury. Urine IL-6, serum IL-6 and serum IL-8 have also been examined as predictors of AKI after bypass requiring surgery in children [25–27], although to a much less extent than other traditional AKI biomarkers. Increased production, reduced renal clearance, and reduced renal metabolism are all proposed mechanisms for the increases in these inflammatory cytokines after AKI [27–29]. Data suggest that IL-6, in particular, is filtered and metabolized by the proximal tubule, and thus increases in the urine during AKI associated with proximal tubular injury and ATN, but with pre-renal azotemia or normally functioning kidneys [27]. Because these AKI biomarkers have been specifically examined in children after bypass requiring surgery, we chose to examine the association of these biomarkers with AKI and a decline in renal NIRS in our cohort.

Immediately following collection, the urine was centrifuged at 3000 rpm at 4 degrees Celsius for 15 minutes. The supernatant was aliquotted into cryovials and stored at –80 degrees Celsius until analysis. The blood was centrifuged at 3500 rpm at 4 degrees Celsius for 10 minutes. The serum was then aliquotted into cryovials and stored at –80 degrees Celsius. At the time of analysis, urine and serum were thawed to room temperature, and the samples were assayed using enzyme linked immunoassay kits from R&D Systems. Cutoff values for biomarkers were based on previously published literature yielding the highest AUC, and are as follows: urine IL-6 > 75 pg/mL; serum IL-6 > 125 pg/mL; serum IL-8 > 40 pg/mL, urine IL-18 > 58 pg/mL, urine NGAL > 220 ng/mL [7, 30, 31].

Demographic and clinical data

Clinical and demographic data collected included age, gender, RACHS-1 score of surgical complexity [32], cardiopulmonary bypass and circulatory arrest time, daily vasoactive inotrope score, duration of mechanical ventilation, intensive care and hospital length of stay and daily urine output.

Statistical Analysis

Data were collected using Research Electronic Data Capture (REDCap)[33]. Between group demographics were compared using Fisher's exact tests and two-sample t-tests for categorical and continuous outcomes, respectively. Multiple logistic regression was used for the primary analysis. There was a minimal amount of missing NIRS data; an average of 0.2% intraoperative and 0.1% postoperative data were missing per subject. Missing data were mostly due to variability in the NIRS monitor sensitivity. NIRS events that occurred before peak biomarker thresholds for AKI were reached were quantified and described using proportions and 95% exact binomial confidence intervals. The associations between occurrence of a NIRS event and a biomarker event (biomarker level above the pre-defined threshold), regardless of temporal order, and adverse outcomes were assessed using two-sample t-tests. Analysis was performed using R version 3.1.1 software (R Foundation for Statistical Computing, Vienna, Austria, <http://www.R-project.org/>).

Results

107 subjects enrolled in the study, and 106 were included in the analysis (Figure 1).. Thirty-four (32%) patients developed AKI; 30 (28%) patients with pRIFLE-R (25% increase in serum creatinine) and 4 patients (3.7%) with pRIFLE-I (50% increase in serum creatinine).

General Outcomes

The patient demographics, operative and postoperative characteristics are presented in Table 1. Patients were categorized into 2 groups 1) patients with < 20% reduction for 20 minutes and 2) patients with a ≥ 20% reduction for at least 20 minutes (a "NIRS event"). There were 12 patients (11.3%) who experienced a NIRS event. While patients who experienced a NIRS event were younger (22 days, 95% CI: 7, 69) than those who did not (78 days, 95% CI: 52, 117), this did not reach statistical significance ($p = 0.09$). There was no difference in gender between the 2 groups ($p = 0.35$). There was a greater proportion of patients with single ventricle physiology who experienced a NIRS event compared to those who did not (No. (%): 8 (67%) vs. 27 (29%)); $p = 0.02$. Surgical complexity was not different between the two groups ($p = 0.33$). Patients who experienced a NIRS event were on cardiopulmonary bypass (139 min, 95%CI: 108, 179) for a significantly longer amount of time than patients who did not (110 min, 95%CI: 101, 121) ($p=0.05$). There was no difference in circulatory arrest time (< 20% 4 (2, 7) vs. ≥ 20%: 10 (4, 17)) or cross clamp time between the two groups ($p = 0.2$ and $p = 0.94$ respectively). Intra-operative urine output did not differ between the two groups ($p = 0.22$). Vasoactive inotrope score, a marker of illness severity, with a higher score indicating increased severity was no different between the two groups at the time of ICU admission ($p = 0.23$) or on the first post-operative day ($p = 0.17$)[34].

Renal Outcomes

Using renal ultrasound, there was no difference in the NIRS kidney depth from the skin between the two groups ($p = 0.12$) nor was there a difference in the maximal kidney depth ($p = 0.89$). Baseline serum creatinine was significantly higher in the group who experienced a NIRS event (0.5 mg/dL; 95% CI: 0.41, 0.62) compared to those who did not (0.35 mg/dL; 95% CI: 0.32, 0.38)($p=0.01$). Peak serum creatinine was significantly higher in the group

who experienced a NIRS event (0.55 mg/dL; 95% CI: 0.45, 0.67) compared to those who did not (0.42 mg/dL; 95% CI: 0.4, 0.45)($p = 0.02$). All patients who developed severe AKI ($n = 3$) were in the group who experienced a less than 20% reduction in renal NIRS. Urine output during the first 6 post-operative hours did not differ significantly between groups ($p = 0.45$). There was no significant difference in urine output from 6–12 hours after surgery, and 12–24 hours after surgery between the 2 groups ($p = 0.82$ and $p = 0.08$ respectively).

We evaluated for a NIRS event in patients who were initially cyanotic, but following repair were acyanotic. In the group who did not have a NIRS event, 28 (30%) were initially cyanotic, compared to 3 (25%) in the group who had a NIRS event ($p = 1$). There was not a significant association between a NIRS event and AKI development, after adjusting for age and single ventricle physiology ($p = 0.51$). The odds of AKI were lower by a factor of 0.62 (95% CI: 0.13, 2.35) for patients who had a NIRS event compared to those who did not. When examining the relationship between a NIRS event and an elevation in each biomarker of AKI above a pre-defined threshold, there was not a significant proportion of decrease in renal NIRS events that occurred in advance of an AKI biomarker increase. Table 2 provides proportions and 95% exact binomial confidence intervals for each biomarker. The proportion of NIRS events preceding biomarker events was very low for all the biomarkers, <6%. Irrespective of timing, a NIRS event and urine IL-18, serum IL-6 and serum IL-8 biomarker event were significantly associated with length of hospital stay; $p = 0.01$, 0.003 and 0.003 respectively. On average, hospital stay was longer for patients who experienced both of these events compared to those who did not, (geometric mean and 95% CI: 23 days (13, 39) vs. 10 days (9, 12), 22 days (14, 36) vs. 10 days (8, 12) and 22 days (14, 36) vs. 10 days (8, 12)). A NIRS event and serum IL-6 and serum IL-8 biomarker event were significantly associated with length of ICU stay, $p = 0.05$ and 0.05. On average, length of ICU stay was longer for patients who had both of these events compared to those who did not, the difference in length of stay was the same for both biomarkers, (geometric mean and 95% CI: 11 days (6, 20) vs. 5 days (4, 6)).

Adverse Clinical Outcomes

Duration of mechanical ventilation was significantly longer in patients who had a NIRS event (58 hours; 95% CI: 32, 106) compared to those who did not (26 hours; 95% CI: 21, 32)($p = 0.05$). In addition, intensive care unit and hospital length of stay were significantly longer in the group who experienced a NIRS event (11 days; 95% CI: 6, 20 and 22 days; 95% CI: 14, 36) compared to those who did not (5 days; 95% CI: 4, 6 and 9 days; 95% CI: 8, 12)($p = 0.05$ and $p = 0.003$). There was no difference in 30-day mortality between the two groups ($p = 1$).

Discussion

This study supports the use of renal NIRS in predicting worse outcomes in children following cardiac surgery with the use of cardiopulmonary bypass. However, we were not able to confirm the utility of renal NIRS for the prediction of AKI in children following cardiac surgery. Several studies have suggested a relationship between a decline in renal NIRS and the development of AKI [19–21], each with its own limitations. Renal NIRS has

been demonstrated to correlate with invasive measures of renal vein saturations [22]. However, normal values for renal NIRS are unknown, especially in cyanotic patients.

The use of renal NIRS as a surrogate for measuring renal regional tissue oxygen saturation has gained popularity over the past decade, in tandem with the recognition that cerebral tissue oxygen saturation monitoring is considered to be the standard of care in the operative and postoperative management of children following cardiac surgery [35]. While renal NIRS is also used in the clinical setting, the output and data trends are variable and often difficult to interpret. Several factors may contribute to this, including the lack of normative data for particular patient populations (i.e., the cyanotic patient with baseline saturations in the 75–85 % range), and sensor positioning. The long-standing question that has been considered is “are we measuring what we say we are?” This can be interpreted in several ways: 1) is the sensor positioned over the target organ and 2) is the target organ sufficiently shallow to allow for adequate depth of penetration of the infrared light. In this study, we measured kidney depth from the skin and maximal kidney depth. The depth of the kidney below the skin was within the manufacturer’s recommendation limits in all patients in this study. We included a group of similarly sized patients, and did not note any differences based on a decline in renal NIRS in the two groups. We suggest that clinicians using renal NIRS assess their placement with renal ultrasound in order to more accurately evaluate kidney presence and depth, and that future clinical trials use ultrasound to guide renal NIRS sensor placement as well.

Only 3 prior studies have evaluated the use of renal NIRS to predict AKI in children following cardiac surgery [19–21]. Overall, these studies predominantly looked at the utility of renal NIRS to predict AKI in children following cardiac surgery, with only 1 study evaluating the use of intra-operative renal NIRS.

Ruf et al, reported a 48% rate of severe AKI (defined by a 50% increase in serum creatinine) in children after cardiac surgery. Notably the rate of AKI is higher than our study population, in which only 3.8% of patients developed severe AKI [20]. Ruf et al., demonstrated a significant correlation between a calculated intraoperative renal NIRS score (which included the baseline value, the current value and the time in minutes, and calculated area under the curve) and the postoperative occurrence of AKI in infants after cardiac surgery. The study also suggested that renal NIRS monitoring performed better than selected biomarkers of renal injury (cystatin C and NGAL) in predicting AKI [20]. In this study, patients with AKI had a significantly longer duration of mechanical ventilation, but there was no difference in intensive care and hospital length of stay. The relationship between the decline in renal NIRS and the intensive care and hospital length of stay was not reported.

Colasacco et al reported that a mean renal NIRS value of less than 75% during the first 24 post-operative hours predicted a 40% increase in serum creatinine with 82% sensitivity and 97% specificity [19]. This group averaged renal NIRS over 24 hours, which limits its clinical use in real time, as serum creatinine may have already started to rise. Additionally, AKI biomarkers have the ability to predict AKI within 6–12 hours, which may have been in advance of evaluating the 24 hour average [4, 7, 36, 37]. The authors did not evaluate secondary outcomes including duration of mechanical ventilation and hospital length of stay.

Owens et al. dichotomized patients into two groups; a low oximetry group, which spent greater than 2 hours below the threshold or 50%, or normal oximetry group which spent less than 2 hours below the threshold. The threshold of 50% was abstracted from previously published data on cerebral oximetry in patients with end organ dysfunction [21]. Patients in this study had severe AKI defined according to pRIFLE-F or an absolute increase in creatinine by 50% [21]. The rate of AKI in the low oximetry group was 50% versus 3.1% in the normal oximetry group. While the authors found that patients in the low oximetry group had a significantly longer duration of mechanical ventilation, there was no significant difference in intensive care and hospital length of stay between the two groups. In comparison to our study, Owens et al used a dramatic decrease in NIRS for an extended period of time, and found it to be a predictor of AKI. In the present study, we examined whether a 20% decline in renal NIRS for 20 minutes would be predictive of AKI, and did not find a significant association. The overall goal of this study was to identify a specific relative drop in renal NIRS that would be clinically useful (able to be recognized in real time versus retrospectively analyzed by area under the curve, use of complex calculations or a prolonged period of monitoring. The lack of association with a 20% decline in renal NIRS for 20 minutes with AKI in our study may be due to a number of explanations including: 1) the low rate of severe AKI in our study, 2) a more significant and prolonged decline in renal NIRS may be necessary to cause AKI and 3) the cause of AKI in our study may not be due to events related to decreased renal perfusion (i.e. nephrotoxic AKI might not be associated with a decline in renal NIRS). Historically, the rate of AKI at our institution has been slightly below the national average [38]. Certain practices at the institution may have lead to the lower rate of AKI; including early institution of diuretics (intermittent or continuous) within the first 12 hours following surgery for avoidance of fluid overload, and relatively short CPB times with continuous ultrafiltration throughout the case. Unfortunately, assessment of fluid overload could not be determined from this study, as reliable daily weights are difficult to obtain in this critically ill population. In addition, differences in the baseline and peak creatinine between the 2 groups (NIRS event versus no NIRS event) may in fact be due to the heterogeneity of the population, and ontologic maturation of the kidneys rather than differences in NIRS. In addition, the study by Owens et al, only included infants, who may be more likely to succumb to AKI following cardiac surgery [21].

Although we did not find an association with AKI, we did find an association with the adverse clinical outcomes. Specifically, we found that the pre-specified outcome of a 20 decrease in renal NIRS for 20 minutes was associated with a longer duration of mechanical ventilation, and a longer intensive care unit and hospital length of stay. It is known that positive pressure ventilation results in decreased systemic venous return, reduced right ventricular filling and overall reduced cardiac output, which leads to a reduction in renal perfusion [39]. Thus, it is plausible that a reduction in renal NIRS being associated with prolonged mechanical ventilation in our study is a consequence of decreased renal perfusion. Since renal NIRS measures renal oxygenation, and is useful in predicting outcomes, it is possible that the duration of decline longer than 20 minutes will be more predictive of AKI when combined with worse clinical outcomes. Thus we believe that further clinical trials evaluating a decline in renal NIRS and worse clinical outcomes are necessary, including the relationship to ventilator mechanics, and how they may impact renal blood flow.

We found that a NIRS event in combination with specific biomarkers (serum IL-6, serum IL-8 and urine IL-18) was associated with a longer intensive care unit and hospital length of stay. Circulating cytokines may have deleterious effects on other organs and higher levels have been shown to be associated with adverse clinical outcomes, including prolonged duration of mechanical ventilation, intensive care and hospital length of stay [26, 40, 41]. IL-8 is a potent neutrophil cytokine that promotes lung neutrophil accumulation and lung tissue injury [42]. Liu et al demonstrated that serum IL-6 and IL-8 are predictive of AKI and prolonged duration of mechanical ventilation in children following cardiac surgery [30]. In a large adult study, AKI biomarkers enhances risk prediction for adverse outcomes in critically ill patients, and it has been suggested that they can be used to estimate prognosis and clinical decision making in for nephrologists and intensivists [41]. Finally, in a pediatric study, the addition of urinary biomarkers improved risk prediction over clinical models alone for prediction of clinical outcomes [40].

Specifically, we found that the pre-specified outcome of a 20 decrease in renal NIRS for 20 minutes was associated with a greater peak creatinine post operatively, longer duration of mechanical ventilation, and a longer stay in the intensive care and hospital. The overall goal of this study was to identify a specific relative drop in renal NIRS that would be clinically useful (able to be recognized in real time versus retrospectively analyzed by area under the curve, use of complex calculations or a prolonged period of monitoring). Although we did not find an association with AKI, we did find an association with the adverse clinical outcomes. The lack of association with a 20% decline in renal NIRS for 20 minutes with AKI in our study may be due to a number of explanations including: 1) the low rate of severe AKI in our study, 2) a more significant and prolonged decline in renal NIRS may be necessary to cause AKI and 3) the cause of AKI in our study may not be due to events related to decreased renal perfusion (i.e. nephrotoxic AKI). Unfortunately, assessment of fluid overload could not be determined from this study, as reliable daily weights are difficult to obtain in this critically ill population. In addition, differences in the baseline and peak creatinine between the 2 groups (NIRS event versus no NIRS event) may in fact be due to the heterogeneity of the population, and ontologic maturation of the kidneys rather than differences in NIRS.

There are several important limitations to this study. Firstly, the majority (28%) of patients with AKI had risk category R, which was not sustained, with only 3.8% having severe AKI. This is even lower than the prior reports of AKI at our institution [38]. We believe that this low rate of AKI may have tempered the capability to demonstrate a possible relationship between a NIRS event and AKI. Secondly, the 20% reduction for 20 minutes may not be significant enough to be associated with AKI despite that we think it is clinically meaningful. It is possible that a greater percent decline for a longer duration would be necessary to predict AKI. Thirdly, we did not measure renal vein saturations in this study, and thus could not determine if ultrasound guided sensor placement and subsequent noninvasive measures correlated with invasive measures. Other markers of tissue oxygen delivery (lactate, SVO2 and cerebral NIRS) and cardiac output were not uniformly available for all study patients, thus limiting power to detect any significant differences in these endpoints. Further studies are necessary to assess these correlations. The biomarkers used in this study are not available for clinical use, with the exception of serum IL-6 and IL-8,

thereby limiting their utility. Finally, while a reduction in renal NIRS may be good at identifying ischemia and hypotension as a cause of AKI, other causes of AKI may not be detected by a reduction in renal NIRS, thereby limiting its use.

Conclusion

In conclusion, a 20% reduction in renal NIRS for 20 minutes during the 24 hours from initiation of cardiopulmonary bypass may be predictive of important clinical outcomes including greater duration of mechanical ventilation, intensive care and hospital length of stay. Although other studies have associated a reduction in renal NIRS with AKI, our study found no association. The reason for this may extend beyond the low rate of AKI, and that a more significant decline over a longer duration of time may be more predictive. The combination of a decline in renal NIRS with specific biomarkers was associated with important clinical outcomes, including a longer intensive care and hospital length of stay. This study serves as a model for future studies, which will be necessary to validate whether a 20% decline in renal NIRS for 20 minutes is associated with adverse clinical outcomes, particularly prolonged mechanical ventilation. Finally, larger multi-center studies gathering a higher rate of severe AKI are necessary to determine the most clinically useful decrease and duration of renal NIRS to demonstrate an association with AKI.

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Figure 1. Patient enrollment and outcome in children undergoing cardiac surgery. *AKI defined by pRIFLE criteria.

Table 1

Demographics and characteristics of patients with an without a decline in NIRS during cardiac surgery

Variable	< 20% decrease (n=94)	20 % decrease (n=12)	p-Value
Age at surgery (days)	78 (52, 117)	22 (7, 69)	0.09
Sex (Female)	38 (40%)	7 (58%)	0.35
Single Ventricle Physiology, n:	27 (29%)	8 (67%)	0.02
NIRS kidney depth from skin (cm)	1 (1, 1)	1 (1, 2)	0.12
Maximal Kidney Depth from skin (cm)	4 (4, 4)	4 (4, 5)	0.89
Operative Characteristics			
RACHS-1 surgical complexity > 3 n:	32 (34%)	2 (17%)	0.33
Cardiopulmonary bypass time (minutes)	110 (101, 121)	139 (108, 179)	0.05
Circulatory arrest time (minutes)	4 (2, 7)	10 (4, 17)	0.2
Cross clamp time (minutes)	65 (52, 79)	64 (27, 101)	0.94
Operative urine output (mL/kg)	9 (8, 11)	7 (4, 12)	0.22
Postoperative Characteristics			
Vasoactive inotrope score at CICU arrival	10 (9, 11)	12 (9, 14)	0.23
AKI: n (%)	31 (33%)	3 (25%)	0.75
Urine output: post hour 0–6 (mL/kg)	2 (2, 3)	3 (2, 4)	0.45
Urine output: Post op hour 6–12 (mL/kg)	2 (2, 3)	2 (1, 3)	0.82
Urine output: Post op hour 12–24 (mL/kg)	2 (1, 2)	2 (2, 3)	0.08
Duration of Mechanical ventilation (hours)	26 (21, 32)	58 (32, 106)	0.05
Intensive Care LOS (days)	5 (4, 6)	11 (6, 20)	0.05
Hospital LOS (days)	10 (8, 12)	22 (14, 36)	<0.01
Death < 30 days: n (%)	1 (1%)	0 (0%)	1
Death > 30 days: n (%)	1 (1%)	1 (8%)	0.21
Cyanotic to Acyanotic: n (%)	28 (30%)	3 (25%)	1
Baseline creatinine (mg/dL)	0.35 (0.32, 0.38)	0.5 (0.41, 0.62)	0.01
Peak creatinine (mg/dL)	0.42 (0.4, 0.45)	0.55 (0.45, 0.67)	0.02

Continuous variables are reported as mean (95% CI), and categorical variables are displayed as the number of subjects and percentage.

Table 2

Relationship between a NIRS event occurring before a peak in serum and urine AKI biomarkers.

Biomarker	Proportion of NIRS events preceding a biomarker event	Exact binomial 95% CI
Urine IL-18	1/85 (1.2%)	(0%, 6.4%)
Urine NGAL	1/34 (2.9%)	(0.1%, 15.3%)
Urine IL-6	3/55 (5.5%)	(1.1%, 15.1%)
Serum IL-6	5/96 (5.2%)	(1.7%, 11.7%)
Serum IL-8	2/76 (2.6%)	(0.3%, 9.2%)

This table demonstrates proportions and 95% exact binomial confidence intervals for each biomarker. The proportion of NIRS events preceding biomarker events (shown in column 2) defined by a 20% reduction in renal NIRS for 20minutes occurring before the biomarker increased above a predefined threshold was very low for all biomarkers (<6%). The probability of a NIRS event preceding a biomarker event is significantly less than 50% for each biomarker.