

## Low Renal Oximetry Correlates With Acute Kidney Injury After Infant Cardiac Surgery

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**Abstract** Acute kidney injury (AKI) is a frequent complication after cardiopulmonary bypass surgery during infancy. Standard methods for evaluating renal function are not particularly sensitive nor are proximate indicators of renal dysfunction that allow intervention in real time. Near-infrared spectroscopy (NIRS) is a newer noninvasive technology that continuously evaluates regional oximetry and may correlate with renal injury and adverse outcomes after cardiac surgery in infants. This prospective observational study enrolled 40 infants (age, <12 months) undergoing biventricular repair. Continuous renal oximetry data were collected for the first 48 postoperative hours and correlated with postoperative course, standard laboratory data, and the occurrence of acute renal injury. Subjects with low renal oximetry (below 50% for >2 h) had significantly higher postoperative peak creatinine levels by 48 h ( $0.8 \pm 0.4$  vs.  $0.52 \pm 0.2$ ;  $p = 0.003$ ) and a higher incidence of AKI (50 vs. 3.1%;  $p = 0.003$ ) than those with normal renal oximetry. These subjects also required more ventilator days and greater vasoactive support, and they had elevated lactate levels. Prolonged low renal near-infrared oximetry appears to correlate with renal dysfunction, decreased systemic oxygen delivery, and the overall postoperative course in infants with congenital heart disease undergoing biventricular repair.

**Keywords** AKI · Congenital heart · Regional oximetry

With improvements in surgical techniques and perioperative care, mortality associated with surgical repair or palliation of infants with congenital heart disease has steadily declined over the past few decades. As a result, recent emphasis has shifted toward minimizing complications and morbidities associated with cardiopulmonary bypass and infant heart surgery. In particular, acute kidney injury (AKI) is common after cardiopulmonary bypass in children, with a reported incidence of approximately 5–20% [7, 13, 14, 17, 20]. Furthermore, AKI is associated with prolonged hospitalization, poor outcome, and increased mortality [2, 6, 20, 27, 34].

Efforts to identify risk factors, earlier diagnosis, and prevention of AKI after cardiac surgery in infancy are of paramount importance. Most AKI classifications such as the Pediatric Renal-Injury-Failure-Loss-End (pRIFLE) stage [3, 4, 29] and the Acute Kidney Injury Network (AKIN) [22, 24] criteria rely on measures of renal dysfunction such as creatinine clearance and oliguria. Although changes in these parameters may reflect renal injury, they are relatively insensitive and late markers of AKI. Also, pRIFLE and AKIN criteria have not been validated after cardiac surgery in infants.

Recently, new urinary and serum biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) [5, 8, 12, 25] and cystatin C [18, 31] have been proposed as earlier markers of kidney injury, potentially facilitating diagnosis and prompt treatment. Although these new biomarkers show some promise, they have not yet been validated in infants after heart surgery, and they do not allow for continuous monitoring of renal function.

Near-infrared spectroscopy (NIRS) is a new continuous, noninvasive technology that measures regional oximetry [30, 33]. The NIRS technology is based on the differential absorption of wavelengths of light by oxygenated and

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deoxygenated hemoglobin. The measured value represents the oxygen content within a local tissue bed.

Cerebral NIRS has been positively correlated with measurements of mixed venous saturation (SvO<sub>2</sub>) [1, 9, 26] and other surrogates of cardiac output.

Low cerebral oximetry (values <45–50% for more than 2 h) during or after cardiac surgery is associated with an increased risk of hypoxic–ischemic injury [32]. In pediatric patients undergoing cardiac surgery, low intraoperative cerebral oximetry has been correlated with decreased cognitive function at 1-year follow-up assessment [21]. In addition, in patients with hypoplastic left heart syndrome, low cerebral NIRS (<55%) in the initial 48 h postoperatively has been a significant predictor of an adverse outcome [28].

The clinical utility of somatic NIRS also has been investigated in a few studies. For example, abdominal NIRS correlated with gastric tonometry in infants after cardiac surgery and was shown to be a predictor for necrotizing enterocolitis in neonates [15]. In another study, multisite oximetry was correlated with lactate levels in patients undergoing surgery for congenital heart disease [10].

Changes in regional oximetry (including renal NIRS) also have been observed after delayed sternal closure and with pericardial tamponade [23]. However, to date, no studies to our knowledge correlate renal oximetry measurements with AKI in infants after cardiac surgery.

The primary objective of this study was to evaluate whether persistent low renal oximetry (<50% for more than 2 h) was associated with AKI (as defined by pRIFLE and other criteria) after cardiac surgery in infants.

## Materials and Methods

Parents or legal guardians of all infants younger than 12 months undergoing planned biventricular repair with cardiopulmonary bypass were approached for consent. The exclusion criteria specified prematurity (postconceptional age,  $\leq 35$  weeks), known genetic or chromosomal disorder, functional single-ventricle anatomy, abnormal renal ultrasound, or preoperative renal insufficiency based on an abnormal serum creatinine for age.

Demographic information including age at operation, preoperative weight, gender, primary cardiac diagnosis, surgical procedure, Risk Adjustment for Congenital Heart Surgery (RACHS-1) [19] classification, length of cardiopulmonary bypass, aortic cross-clamp time, time to extubation, and circulatory arrest time was recorded.

In the operating room or immediately at arrival in the cardiothoracic intensive care unit postoperatively, a pediatric-sized oximetry sensor was placed on the right flank below the costovertebral angle overlying the right kidney.

An INVOS 5100B oximeter (Somanetics Corp, Troy, MI, USA) was used to monitor renal oximetry. Regional oximetry was collected (in 20-s intervals) for the initial 48 h after surgery, and the primary caregivers were blinded to the results.

The patients were dichotomized into “low oximetry” or “normal oximetry” groups based on the total time ( $\geq 2$  vs.  $< 2$  h, respectively) each patient spent below an oximetry threshold of 50%. This threshold was chosen based on previous cerebral oximetry data suggesting correlation of prolonged low oximetry with end-organ dysfunction [11, 32]. Comparisons of demographic, operative, postoperative, and hospital course data, including assessment of renal function and secondary clinical variables (e.g., lactate and inotropic score), were made between groups.

The primary outcome of AKI was defined as meeting “failure” under pRIFLE criteria (creatinine clearance,  $< 35$  ml/min) or having an absolute increase in creatinine by 0.4 mg/dl and at least 50%. This second definition of AKI was based on evolving data suggesting that small changes in creatinine may indicate kidney injury in infants undergoing cardiopulmonary bypass (CPB) [35] and that pRIFLE may not be appropriate in this population. Sentinel events, such as the need for extracorporeal membrane oxygenation (ECMO) or dialysis, and mortality also were recorded.

Physiologic data were expressed as mean  $\pm$  standard deviation. An unpaired two-tailed *t*-test was used to compare continuous data between groups. Fisher’s exact test was used for dichotomous values.

## Results

The study enrolled 40 neonates and infants undergoing cardiac surgery resulting in biventricular repair. The diagnoses and surgical repairs are listed in Table 1. The two most frequent diagnoses were tetralogy of Fallot (TOF) and d-transposition of the great arteries (d-TGA) (Table 1). No major intraoperative complications were found. The demographic characteristics are reported in Table 2. The mean age at operation was 81 days, and 65% of the patients were male.

The predefined criteria for low renal oximetry were met by eight patients as follows: TOF ( $n = 6$ ), d-TGA + coarctation ( $n = 1$ ), and truncus arteriosus ( $n = 1$ ). The remaining 32 patients were classified in the normal renal oximetry group. On the average, the low oximetry group spent 13% (6 h) of the initial 48 postoperative hours below 50% compared with less than 1% (0.47 h) for the normal oximetry group ( $p < 0.005$ ).

Comparisons of demographic and baseline clinical variables between groups are shown in Table 2. The groups did not differ statistically in age, weight, or RACHS-1

**Table 1** Diagnoses and operations performed

Diagnoses	Procedures
TOF ( <i>n</i> = 11)	Complete TOF repair ( <i>n</i> = 11)
D-TGA/IVS ( <i>n</i> = 5)	Arterial switch operation ( <i>n</i> = 5)
D-TGA/VSD/PS ( <i>n</i> = 3)	Rastelli ( <i>n</i> = 3)
D-TGA/VSD/IAA ( <i>n</i> = 2)	Arterial switch operation with arch repair ( <i>n</i> = 2)
Double chamber RV ( <i>n</i> = 3)	RV muscle bundle division ( <i>n</i> = 2), Rastelli ( <i>n</i> = 1)
DORV ( <i>n</i> = 3)	VSD closure ± RVOT muscle division ( <i>n</i> = 2), Rastelli ( <i>n</i> = 1)
IAA/VSD ( <i>n</i> = 2)	Norwood/Rastelli ( <i>n</i> = 1), arch repair/VSD closure ( <i>n</i> = 1)
VSD ( <i>n</i> = 2)	VSD closure ( <i>n</i> = 2)
Aortic stenosis ( <i>n</i> = 2)	Ross ( <i>n</i> = 1), Ross/Konno ( <i>n</i> = 1)
AVSD ( <i>n</i> = 2)	AVSD complete repair ( <i>n</i> = 2)
Coarctation ( <i>n</i> = 1)	Arch repair ( <i>n</i> = 1)
TAPVR ( <i>n</i> = 1)	Repair of TAPVR ( <i>n</i> = 1)
Ebstein’s anomaly ( <i>n</i> = 1)	Tricuspid valve replacement ( <i>n</i> = 1)
Truncus arteriosus ( <i>n</i> = 1)	VSD closure and RV-PA conduit ( <i>n</i> = 1)
ALCAPA ( <i>n</i> = 1)	Reimplantation of LCA ( <i>n</i> = 1)

TOF tetralogy of Fallot, dTGA/IVS transposition of the great arteries with intact ventricular septum, VSD ventricular septal defect, PS pulmonary stenosis, IAA interrupted aortic arch, RV right ventricle, DORV double-outlet right ventricle, RVOT right ventricular outflow tract, AVSD atrioventricular septal defect, TAPVR total anomalous pulmonary venous return, ALCAPA anomalous left coronary artery from pulmonary artery, LCA left coronary artery

**Table 2** Demographics, operative data, and overall outcomes

	Total ( <i>n</i> = 4)	Low oximetry ( <i>n</i> = 8)	Normal oximetry ( <i>n</i> = 32)	<i>p</i> value <sup>a</sup>
Age at operation: days (range)	81 (5–330)	56 (5–165)	87 (5–330)	0.36
Weight: kg (range)	4.8 (2.4–88)	4.5 (3.2–6.8)	4.85 (2.5–8.8)	0.54
Female: <i>n</i> (%)	14 (35)	3 (38)	11 (34)	1
RACHS-1 >3: <i>n</i> (%)	9 (23)	2 (25)	7 (22)	0.59
CPB (min)	97 ± 43	115 ± 37	92 ± 44	0.19
Circulatory arrest: <i>n</i> (%)	5 (12.5)	1 (20)	4 (11)	0.57
Aortic cross clamp (min)	54 ± 28	59 ± 32	52 ± 28	0.63
ECMO: <i>n</i> (%)	1 (2.5)	1 (20)	0	0.12
Death: <i>n</i> (%)	1 (2.5)	1 (20)	0	0.12

RACHS-1 risk assessment for congenital heart surgery, CPB cardiopulmonary bypass, ECMO extracorporeal membrane oxygenation

<sup>a</sup> *p* values comparing low and normal oximetry groups based on Student’s *t*-test for continuous variables and Fisher’s exact test for dichotomous variables. Continuous variables are reported as a mean ± standard deviation, whereas dichotomous variables are displayed as number of patients and percentage

score. In addition, there was no statistical difference in CPB time, aortic cross-clamp time, or use of circulatory arrest between the cohorts.

One patient in the low oximetry group required ECMO support and eventually died on postoperative day 11 after failing to wean from ECMO support. Another patient in the normal oximetry group was resuscitated and fully recovered from a cardiac arrest.

The primary and secondary outcome data are shown in Table 3. A total of five patients (12.5%) experienced AKI

based on pRIFLE creatinine criteria for “failure,” and 10 patients (25%) had an increase in creatinine by at least 0.4 mg/dl and 50%. Only one patient (low oximetry group) required renal replacement therapy. Findings showed that 63% of the patients (*n* = 5) with low renal oximetry experienced AKI based on our definition versus 16% (*n* = 5) of the patients with normal renal oximetry (*p* = 0.015).

According to pRIFLE, 50% of the patients (*n* = 4) with low oximetry compared with 3.1% of the patients (*n* = 1)

**Table 3** Incidence of acute kidney injury (AKI) and evaluation of secondary clinical variables between low and normal oximetry

	Low oximetry ( <i>n</i> = 8)	Normal oximetry ( <i>n</i> = 32)	<i>p</i> value <sup>a</sup>
AKI (pRIFLE): <i>n</i> (%)	4 (50)	1 (3.1)	0.003
AKI ( $\Delta$ Crt >0.4 and >50%): <i>n</i> (%)	5 (63)	5 (16)	0.002
Renal replacement therapy: <i>n</i> (%)	0 (20)	0	0.12
Mechanical ventilation (days)	7.6 $\pm$ 3.6	4.2 $\pm$ 2.9	0.008
Hospital length of stay (days)	15.4 $\pm$ 5.7	12.7 $\pm$ 11	0.51
Peak creatinine	0.83 $\pm$ 0.4	0.52 $\pm$ 0.2	0.003
Peak lactate	4.7 $\pm$ 4.2	2.9 $\pm$ 2.0	0.08
Average lactate	3.0 $\pm$ 2.5	1.5 $\pm$ 0.7	0.004
VIS peak	23.6 $\pm$ 17	13.8 $\pm$ 8.8	0.03

VIS vasoactive inotropic score

<sup>a</sup> *p* values are based on Student's *t*-test for continuous variables and Fisher's exact test for dichotomous variables. Continuous variables are reported as mean  $\pm$  standard deviation, whereas dichotomous variables are displayed as number of patients and percentage

with normal oximetry met the criteria for acute renal failure based on a creatinine clearance of less than 35 ml/min ( $p = 0.003$ ). The low oximetry patients had a nearly two-fold increase in length of mechanical ventilation compared with normal oximetry patients (7.6 vs. 4.3, respectively;  $p = 0.009$ ), but total hospitalization days did not differ between the two groups (Table 3).

Additionally, peak creatinine was significantly higher in the low oximetry group than in the normal group (0.83  $\pm$  0.4 vs. 0.52  $\pm$  0.2;  $p = 0.003$ ). The low oximetry cohort also had higher average lactate levels (3.0  $\pm$  2.5 vs. 1.5  $\pm$  0.7;  $p = 0.004$ ) and the maximum vasoactive inotropic score (VIS) [16] (23.6  $\pm$  17 vs. 13.8  $\pm$  8.8;  $p = 0.03$ ) within the first 24 h compared with the normal oximetry group (Table 3), suggesting a more critical clinical status.

## Discussion

Acute kidney injury continues to be a significant complication of CPB and cardiac surgery in children and infants, resulting in increased morbidity and mortality [6, 7, 27]. Consequently, early detection and correction of aberrations in kidney function and perfusion are essential for the management of these critically ill patients. Not only are the criteria for the diagnosis of AKI in this population evolving, but new diagnostic tools and techniques also are continually under investigation. To our knowledge, this is the first study to associate low renal oximetry with acute kidney injury in pediatric patients undergoing biventricular repair for congenital heart disease.

Typically, renal function is evaluated with serum creatinine level (or creatinine clearance) and urine output, leading to the development of diagnostic criteria such as pRIFLE and AKIN (acute kidney injury network). Unfortunately,

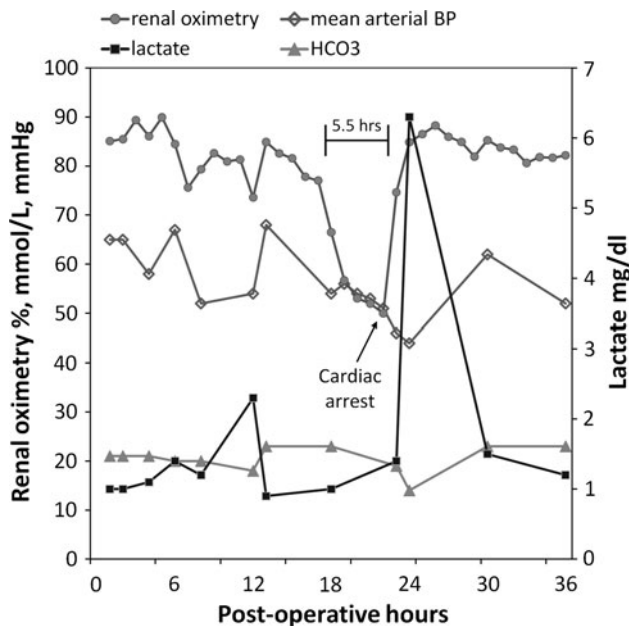
changes in both of these markers may be delayed as much as 48–72 h after renal injury.

The low renal oximetry values in this study were observed mainly in the first 24 h postoperatively, with serum creatinine typically peaking by 48 h. Thus, renal NIRS may have the unique ability of providing early real-time data regarding regional oxygenation that may serve an important role in monitoring renal perfusion and the effectiveness of interventions aimed at preventing or reversing renal injury.

Notably, cerebral oximetry measured in the study patients did not correlate as strongly with AKI or low renal oximetry, suggesting the importance of regional monitoring.

Although many studies analyzing regional oximetry are focused on the acute or chronic effects of ischemia on end-organ function, there may be an added benefit of monitoring regional oximetry above and beyond the traditional clinical parameters typically monitored in an intensive care unit (ICU) setting.

In our study, one patient (in the normal oximetry group) had an acute cardiorespiratory arrest during the monitoring period after an initial 24 h of stability. This patient displayed no apparent signs of compromise based on standard clinical parameters or intermittent laboratory tests (Fig. 1). However, 5 h before the arrest, a significant drop in regional oximetry was observed, which persisted until the arrest. It was not until after the arrest episode that alterations in his vital signs and serum markers of impaired oxygenation (i.e., lactate, HCO<sub>3</sub>) were clearly identified. This change in oximetry was reversed with resuscitation, as were the standard clinical parameters (Fig. 1). Although this is only one case example, it suggests that continuous somatic oximetry may prove useful for identifying silent changes in oxygen delivery earlier than standard monitoring approaches and may be used to prevent cardiovascular collapse.



**Fig. 1** Case of an 8-month-old boy with tetralogy of Fallot after complete repair. The boy was extubated, with normal blood pressure, normal serum bicarbonate and lactate levels, and renal oximetry values above 80%. As shown in the graph, renal oximetry dropped 13 h after surgery without significant changes to the other parameters, and 5½ h later, the boy had a cardiopulmonary arrest (arrow). Elevation in lactate and decreases in bicarbonate and blood pressure then became apparent. After resuscitation, all parameters normalized

This study was limited by its small sample size and by the enrollment criteria that included only complete biventricular repairs. A larger cohort including more complex congenital heart lesions (e.g., functional single ventricles) may have had a higher incidence of AKI, allowing for more robust statistical analysis.

Unfortunately, although estimated thresholds for “normal” regional oximetry exist in fully saturated patients, we are not aware of any criteria for abnormal regional oximetry in hypoxemic patients with palliated congenital heart disease and residual right-to-left shunts. Therefore, we chose not to include these patients in this initial study.

In addition, no consensus definition exists for AKI in infants and children undergoing cardiac surgery. Application of pRIFLE or AKIN criteria to this patient population may not be appropriate because the mechanism for acute kidney injury (i.e., CPB) is very different from that in other patient populations for which these criteria may be useful. Investigations are currently underway at our institution to define AKI more carefully in infants and children undergoing CPB surgery.

In summary, low renal oximetry, at least as defined in this study, appears to be associated with AKI, worse clinical status, and increased length of mechanical ventilation in neonates and infants after biventricular repair of congenital heart disease. Persistently low renal oximetry also

may be a harbinger of impending cardiovascular collapse in these same subjects. As a noninvasive technology that provides continuous real-time output, regional oximetry may eventually prove to be an essential part of postoperative care in the pediatric cardiac intensive care unit.

Additional prospective randomized controlled trials are being designed to evaluate whether interventions aimed at improving regional oximetry can prevent the development of end-organ dysfunction. These types of prospective interventional studies are absolutely crucial toward understanding the true clinical utility of this innovative monitoring approach.

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