ADULT RENAL NEAR INFRARED SPECTROSCOPY AND OXYGEN DELIVERY DURING CPB: CORRELATIONS TO PREVENT ACUTE KIDNEY INURY

By

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Abstract

A major complication associated with cardiopulmonary bypass (CPB) is acute kidney injury (AKI), with around 30% of patients experiencing some sort of renal insult (31). Kidney performance is strongly linked to cardiac performance, so perfusionists can play a major role in implementing strategies to reduce the incidence of AKI. The use of Near Infrared Spectroscopy (NIRS) has been validated for the use of cerebral oximetry for both pediatric and adult patients, unlike somatic monitoring where only pediatric randomized control trials have proven to be successful. Since the distance from sensor to organ for adults is greater than 1.4 centimeters, there are not any studies to correlate perfusion parameters to adult renal oximetry. The primary goal of this pilot study was to correlate renal oximetry values to pre-established perfusion outcome markers that are routinely measured during CPB. In this way, renal NIRS may be used as a real time trending device to help prevent AKI. The INVOS™ system was used for both cerebral and renal NIRS monitoring. Renal oximetry pads were placed between the 11th-12th intercostal spaces and the most accurate baseline rSO_2 (regional oxygen saturation) level was obtained before sedating the patients. Baseline variables obtained were: age, weight, height, body surface area, history of diabetes, ejection fraction, creatinine, hemoglobin, hematocrit, cerebral oximetry, renal oximetry, and lactate values. Operative variables obtained were: hemoglobin, mean arterial pressure, pump flow, cardiac index, cerebral oximetry, renal oximetry, lactate, temperature, venous oxygen saturation, and oxygen delivery. A multivariable statistical analysis model was used to correlate the data. The results showed the strongest statistical correlations of renal oximetry with hemoglobin ($p<0.01$, $p=0.01$), cardiac index ($p<0.0001$, $p<0.01$), and oxygen delivery ($p<0.0001$, $p<0.0001$). The higher these variables were, the higher the renal oximetry values and vice versa. The changes in oxygen delivery were correlated to the changes in renal oximetry values. Specifically as the DO2 increases 1.15 mL/min1/m2 ($p<0.01$), the percent change in the left renal oximetry increases 1%. As for the right renal, when the DO2 increases 0.94 mL/min1/m2 ($p<0.01$), the percent change in the

right oximetry increases 1%. A renal oximetry value with a decrease of more than 20% from pre-operative baseline is associated with a significantly lower DO2 than renal oximetry values without a decrease more than 20% from pre-operative (p=0.01). The DO2 difference was calculated at 21.97 ml/min1/m2. There is a direct correlation between oxygen delivery values and renal oximetry saturation values. In conclusion, this pilot observational study has shown the INVOS™ system to be a valuable real-time trending device for renal oximetry saturation values with perfusion parameters to help prevent or reduce acute kidney injuries for cardiopulmonary bypass patients.

Background and Significance of Study

According to the CDC, thousands of people a day are having heart surgery around the US. The total is estimated around 600,000 people annually (20). There are many complications and risk factors for open heart surgery and use of cardiopulmonary bypass (CPB). Specifically we are focusing on acute renal failure (ARF) which affects patient outcomes, increases length of stay, and increases morbidity and mortality. Despite an increasing population of 'high risk' patients, the mortality following cardiac surgery has decreased in recent years. However, the incidence of postoperative ARF remains virtually unchanged (26). CPB is known to cause renal damage; total CPB time >140 min, and mean perfusion pressure below 60 mmHg both increase the risk of developing ARF (36). It is estimated that about 3-8% of patients undergoing CPB will develop ARF, depending on their pre-operative kidney condition (24). However about 30% will experience some sort of renal insult which can either resolve or worsen. When a dialytic treatment is required the mortality rate may reach 50% (31). The kidney performance is strictly linked to cardiac performance, in fact the kidneys, although their combined weight is less than 1% of total body weight, normally receive 20-25% of the cardiac output. A low cardiac output (i.e. pump flow) during surgery, decreases dramatically the renal perfusion pressure and activates a number of renal vasoconstrictor systems (sympathetic nervous system, renin-angiotensin system, and vasopressin secretion) which damage indirectly the kidneys (9). The renal medulla receives <10% of renal blood flow, but is responsible for around 90% of renal oxygen extraction; which makes it particularly susceptible to hypoxia. The renin–angiotensin system regulates renal blood flow and pressure to maintain a constant glomerular filtration rate, however CPB enhances this process which augments renal vasoconstriction and results in renal hypo-perfusion and loss of auto-regulation (36).

Chertow et al provided a study that included 42,773 patients undergoing open heart surgery with CPB and evaluated them to determine the association between acute renal failure sufficient to require dialysis and operative mortality, with and without adjustment for comorbidity and postoperative

complications. ARF in this study was defined as increased serum creatinine 50% or greater from baseline. In this study 1.1% (460) patients developed ARF. Overall operative mortality was 63.7% in these patients, compared with 4.3% in patients without this complication. Adjustments for comorbid factors were made including: surgery type, baseline renal function, preoperative intra-aortic balloon pump, prior heart surgery, NYHA class IV status, peripheral vascular disease, pulmonary rales, left ventricular ejection fraction below 35%, chronic obstructive pulmonary disease, systolic blood pressure, and the cross-product of systolic blood pressure and surgery type. More adjustments were made for seven postoperative complications: low cardiac output, cardiac arrest, perioperative myocardial infarction, prolonged mechanical ventilation, reoperation for bleeding or repeat CPB, stroke or coma, and mediastinitis. Even after adjusting for all these conditions, Chertow et al found that ARF was independently associated with early mortality following cardiac surgery. Interventions to prevent or improve treatment of this condition are urgently needed.

In the past there have been discrepancies on the diagnosis and definition of ARF. Because of this; more defined classification systems have been developed. Today the two most common are the RIFLE and AKIN models (9).

Table1: Classification Systems

Stage	Serum creatinine criteria	Urine Output Criteria
1	Increase in serum creatinine of more than or equal to 0.3 mg/dl or increase to more than or equal to 150% to 200% (1.5-to 2-fold) from baseline	Less than 0.5 ml/kg per hour for more than 6 hours
2	Increase in serum creatinine to more than 200% to 300% (> 2-to3-fold) from baseline	less than 0.5 ml/kg per hour for more than 12 hours
3	Increase in serum creatinine to more than 300% (> 3-fold) from baseline (or serum creatinine of more than or equal to 4.0 mg/dl with an acute increase of at least 0.5 mg/dl)	Less than 0.3 ml/kg per hours for 24 hours or anuria for 12 hours

AKIN Modified from Metha et al

	GRF criteria	Urine output criteria
Risk	Serum creatinine increased 1.5 times or GFR decrease > 25 %	< 0.5 ml/kg/h for 6 h
Injury	Serum creatinine increased 2.0 times or GFR decrease > 50 %	< 0.5 ml/kg/h for 12h
Failure	Serum creatinine increased 3.0 times orGFR decrease > 75 % or creatinine > 4 mg/dl (Acute rise > 0.5 mg/dl)	< 0.3 ml/kg/h for 24 h or anuria for 12 h
Loss	Persistent acute renal failure; complete loss of kidney function for longer then 4 weeks	
End-stage renal disease	End stage renal disease for longer than 3 months	

RIFLE scale modified by Bellomo et al.

According to Bove et al. major advantages of the AKIN model are:

1. More flexible interim classification of the renal failure: patient on RRT is stage 3 regardless of severity class at the time RRT was started.
2. More accurate detection of AKI.

Using the RIFLE classification, the incidence of AKI after cardiac surgery is much higher than previously reported incidence of ARF. Bove et al defines this process in four ways:

1. Decreased renal perfusion
2. Ischemic, toxic, or obstructive insult of renal tubule
3. Tubule-interstitial process with inflammation and edema
4. Primary reduction of the glomerulus filtering capacity

Kidney injuries are divided into three categories: Pre-renal (50%), intra-renal (40%), and post-renal (10%) (36). This is important in establishing the problem and implementing a solution. Pre-renal or pre-renal azotemia (high BUN) is associated with anything that prevents adequate blood flow to the kidneys. This includes anything from decreases in CO, systemic vasodilation, and intravascular volume depletion. The second most common insult is within the kidney, intra-renal. This includes anything from prolonged vasoconstriction, toxicity from drugs or contrast dyes, vascular disease (renal artery stenosis), and inflammation (SIRS). Post-renal could be anything that causes a blockage past the kidneys such as kidney stones.

Clinically we use serum creatinine and BUN levels for renal monitoring. As a general rule clinicians can use the BUN to Creatinine ratio as a tool to determine the area of possible insult. A

BUN/Creatinine ratio of >20:1 and high urine osmolality is indicative of Pre-renal dysfunction. Whereas a BUN/Creatinine ratio of <15:1 and a low urine osmolality is more indicative of intra-renal dysfunction (36).

During CPB, macro and micro embolic insults to the kidney, release of catecholamines and inflammatory mediators, increases in vascular resistance and decrease in glomerular filtration rates of 25-75%, all lead to risk factors for developing AKI (9). One possible way perfusionists can manipulate and improve these factors is through the use of pulsatile flow (26). Just as with hemolysis, a certain degree of renal injury is inevitable after CPB surgery. The resultant injury, even in the mildest form, is an independent variable predicting mortality. In order to minimize the effects of CPB on kidneys, numerous pharmacological and non-pharmacological renal protection strategies have been tested. One strategy is to maintain pulsatile perfusion, which closely conforms to the normal heart beat as compared to non-pulsatile CPB. Pulsatile flow is initiated upon arresting the heart and application of the aortic cross clamp. Arresting the heart provides a quiescent period for the surgeon to have a motionless heart for the best surgical repairs. Subsequently, pulsatile flow is ended upon cross clamp removal. Pulsatile flow during CPB has been shown to provide higher hemodynamic energy per second compared to non-pulsatile flow at equivalent mean arterial pressure and pump flow rate (1). Maintaining pulsatile perfusion during CPB has been shown to attenuate the pathologic effects of surgery by lowering peripheral vascular resistance, maintaining better micro-circulation and tissue metabolism, and decreasing tissue edema (1).

Sievert et al performed a meta-analysis analyzing if there are any renal benefits of pulsatile perfusion to CPB. This study found that pulsatile perfusion resulted in greater creatinine clearance and reduced post-operative lactate levels compared with non-pulsatile perfusion, suggesting that pulsatile perfusion is beneficial in renal preservation and increases oxygen delivery to the tissues. From the

results they hypothesized that selected patients at a high risk for renal failure following CPB may especially benefit from the use of pulsatile perfusion to maximize renal blood flow (35).

There are conflicting ideas on the use of pulsatility and the issue of hemolysis in the perfusion cohort. Differences from institutional practices and equipment used created this over time. A meta-analysis done by Long et al. found no significant difference between roller and centrifugal pumps in any variable measured, including plasma free hemoglobin. A properly occluded roller pump has been shown to have no difference in plasma free hemoglobin as compared to a centrifugal pump (26). We know there is some degree of hemolysis during CBP. Several studies indicated that some forms of pulsatile flow are no more damaging to red blood cells and platelets than nonpulsatile flow (2). Roller pumps use a module that spins the roller head in a pulsatile pattern, creating pulsatile flow and can be measured using the pulse pressure of the patient's arterial pressures. Centrifugal pumps are afterload dependent and create pulsatility in different manners. The two most common are the use of intra-aortic balloon pump to create the pulse or the intermittent speeding up and slowing down of the revolutions per minute pump flow.

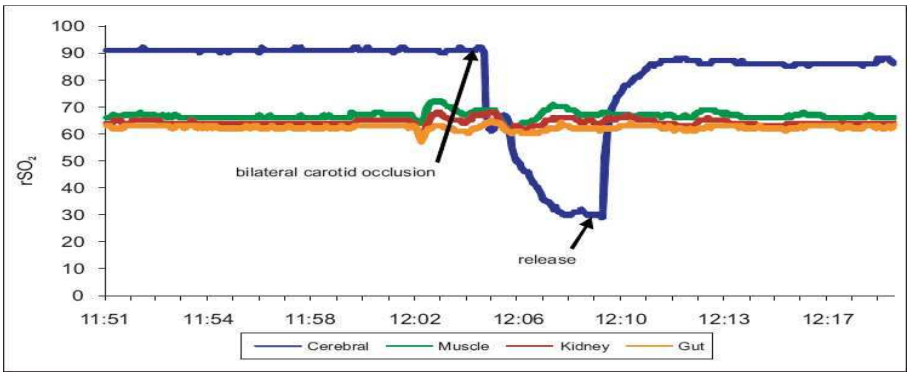
NIRS

The use of Near Infrared Spectroscopy (NIRS) has become a widely used tool in the analysis of tissue hemoglobin saturation in vivo, allowing early detection and correction of imbalances in oxygen delivery to the brain and vital organs (8). Early devices measured hemoglobin saturation just under the surface since visible light cannot penetrate very far. They were accurate but could only measure the capillary blood in the skin. The use of NIR light of 700-1000nm wavelength are based on the fact that very few substances in tissue absorb NIR light, allowing for deeper penetration (8). The main substances that can create noise for NIR readings are cytochrome, myoglobin, and hair. Cytochrome enzymes absorb NIR light but the tissue concentration is an order of magnitude lower than hemoglobin. Metalloproteins with porphryin rings are the only biologic structures that absorb much NIR light and

hemoglobin molar absorptivity at these overtone wavelengths is too low. As well, myoglobin desaturation is limited allowing analysis of saturated hemoglobin to be specific (39). The extremely low level of absorption of NIR light by hemoglobin is the dominant factor in achieving accurate measurements, requiring low light intensity in order to avoid overwhelming the signal and a very low level of noise; thus producing a high signal to noise ratio (32). Noise reduction remains to be the most important factor in improving accuracy and precision in vivo (30). INVOS™ technology includes contributions in a 3:1 ratio, yielding a venous-weighted percent saturation. The INVOS™ system uses near-infrared light at wave lengths of 730-810nm that are absorbed by hemoglobin. Light travels from the sensor's light emitting diode to a proximal and distal sensor. This allows separate data processing of shallow and deep optical signals. This 3:1 ratio is computed from the area under the curve between the proximal and distal sensors (32). This provides real-time data about the balance or imbalance of oxygen supply and demand, thus reflecting venous oxygen reserve; the oxygen remaining after extraction by tissues and vital organs. Decreases in venous oxygen reserve can be a warning of developing pathology and deteriorating patient condition (32). This weighted reading provides a regional hemoglobin oxygen saturation (rSO2).

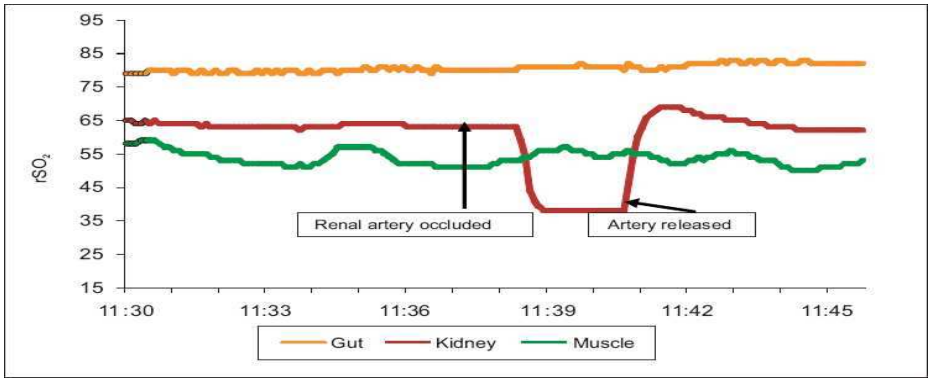
NIRS has been used extensively in cardiac surgery to monitor oxygen delivery to the brain and spinal regions in adults, children and infants. This technology has been used to prevent potentially catastrophic incidents such as accidental cannula misplacement (10,14,16,19,29). Accuracy and validation of oxygen delivery specifically to brain tissue is done by altering partial pressure of carbon dioxide in the arterial blood to increase cerebral perfusion which in turn increased NIRS monitoring numbers (25). In Hoffman et al the cerebral arteries were occluded in a piglet and the NIRS monitoring showed rapid changes while other clinical measures remained steady (22).

Figure 1: Carotid Occlusion; Cerebral Oximetry (22)



Somatic monitoring is another challenge on its own. The NIR light penetrates potentially thick muscle and fascia layers when applied to other body surfaces. Animal experiments have demonstrated that when the skin to organ distance is less than 1.4cm (by the INVOS system), changes in flow to the organ are reflected in immediate and sensitive changes in the rSO2 (22,40). Hoffman et al. showed when the renal artery in piglets was clamped, again the NIRS monitoring in the renal area was immediately reflected.

Figure 2: Renal Artery Occlusion; Renal Oximetry (22)



The use of perirenal monitoring as an indicator of peripheral perfusion has been well established in hemodynamic management of infant and neonatal congenital heart patients in the operating rooms (4,5,7,17,18). Cerebral and somatic monitoring has been used routinely in infants during cardiac surgery. Ruf et al's prospective study with NIRS renal monitoring and CPB surgery suggest that

prolonged low renal oximetry values during cardiac surgery correlate with the development of AKI and may be superior to conventional biochemical markers in infants undergoing CPB (34).

With the use of NIRS it is imperative to remember that rSO2 is a venous weighted reading and responsive to all the physiologic factors that influence oxygen availability such as anatomical variability, hemoglobin dissociation, cardiac output, dyshemoglobinemias, blood pH, vascular permeability and metabolic demand, all resulting in an AV difference (8).

NIRS has been clinically proven to be an accurate indicator to help prevent AKI and monitor renal perfusion in pediatrics (32). Since we are approaching the upper limit of 1.4cm distance from sensor to kidney in adults, there have not been any real studies to show its effectiveness in adults. We want to show that this technology can be used to monitor a trend to help prevent AKI in the adult population.

Oxygen Delivery

Ranucci et al. provided evidence that the degree of hemodilution during CPB was an independent risk factor for acute renal failure after cardiac operations (31). In their prospective observational study they investigated the role of the lowest (nadir) oxygen delivery, lowest hematocrit, and lowest pump flow during cardiopulmonary bypass as possible risk factors for acute renal failure and renal dysfunction. Their results showed that the best predictor for acute renal failure and peak postoperative serum creatinine levels was the oxygen delivery, with a critical value at 272 mL/min/m2. The hematocrit was an independent risk factor with a lowest predictive value at a cutoff of 26%. When corrected for needs of transfusions, only the lowest oxygen delivery remained an independent risk factor. A high degree of hemodilution during cardiopulmonary bypass is a risk factor for postoperative renal dysfunction; however, its detrimental effects may be reduced by increasing the oxygen delivery with an adequately increased pump flow. Arterial CPB oxygen delivery was calculated by:

DO2=pump flow indexed x (hemoglobin x 1.36 x hemoglobin saturation + 0.003 x arterial oxygen tension) x 10 (30). A further abbreviated formula can be derived using: *DO2= 13.4 x HBG x CI* achieving the same oxygen delivery amount in mL/min/m2, assuming 100% saturation.

Ranucci et al.'s study included 1,048 patients and excluded patients already on dialysis treatment. ARF was defined as the need for renal replacement therapy (RR-ARF) and secondary endpoint as peak postoperative serum creatinine (PPSC). Statistical significance was found in: Age, Baseline serum creatinine, Diabetes, COPD, CPB duration, Pump flow indexed, lowest hematocrit, and lowest oxygen delivery. All the patients were kept between 32-34C. Hematocrit levels were measured preoperatively and if less than 30% patients received blood, during CPB less than 22% they received blood, and postoperatively less than 22% they received blood (31). However Ranucci et al's study did not report lower temperatures, lactate levels, or SVO2 monitoring.

Magruder et al. at Johns Hopkins conducted a pilot goal-directed perfusion initiative based on oxygen delivery to try to reduce the incidence of AKI during CPB. The pilot study included 88 patients receiving goal directed perfusion. They analyzed 5,225 patients undergoing cardiac surgery on CPB at their institution between 2010-2015. A control group of 88 patients were selected and well matched across most baseline and operative variables. Once on CPB the DO2 was sought to be maintained greater than 300 ml O2/min/m2. This nadir DO2 was chosen by Magruder et al to safely maintain above previous published values 242-272 ml/min/m2 (27,31). Other parameters used for the goal directed perfusion (GDP) group: 3/8" venous vs. 1/2", continual z-buff, low prime volume Sorin Inspire oxygenator, restricted mannitol use, limited rewarming to 1C every 5 minutes, limited vasopressor use, limited RAP volumes, and continual heparin administration. The Johns Hopkins study authors concluded that nadir DO2 on CPB was lower in the control group than GDP cohort patients (240 vs. 302 mL/min/m2 BSA, P <.001), and this appeared to be driven by higher pump flow indexes (1.9 vs. 2.4 L/min/m2, P<.001) as opposed to differences in nadir hemoglobin concentrations on CPB (9.0 vs. 8.7, P= 0.46). The

incidence of AKI stage 1 or greater was higher in controls than GDP patients (23.9% vs. 9.1%, P= 0.008). Although the degree of AKI was predominantly AKI stage 1 (i.e., 50%-100% increase in serum creatinine from baseline), this difference between control and GDP AKI incidences also persisted when analyzing the data across all 3 stages of AKI (chi-square P= 0.03). The median percent increase in serum creatinine over the first 72 postoperative hours was higher in controls (27% vs. 10%, P<.001). In a subgroup analysis, they also compared changes in creatinine from baseline among only patients with preoperative GFR less than 90 mL/min and less than 60 mL/min, and found that significant differences in median serum creatinine increases persisted (GFR<90,22% vs. 9%, P= 0.001; GFR<60, 40% vs. 9%, P= 0.04) (27). Separating out the differences in GFR patients is very significant because it identifies between healthier kidney patients and known kidney insult patients (either acute or chronic). Below is Magruder et al breakdown of AKI incidence between both groups.

Table 2:
Outcomes of control and goal-directed perfusion patients (27)

Incidence of AKI (50% increase from base)	23.9 (21)	9.1 (8)	.008
AKIN 0 (no AKI)	76.1 (67)	90.9 (80)	.03
AKI stage 1 (50%-100% or ≥0.3 increase)	19.3 (17)	5.7 (5)	
AKI stage 2 (100%-200% increase)	3.4 (3)	3.4 (3)	
AKI stage 3 (>200% increase or HD)	1 (1.1)	0	
Median % Cr increase from baseline (IQR)	27 (11-48)	10 (0-27)	<.001
Only patients with preoperative GFR <90 mL/min (No. of pts)	51	58	
Median % Cr increase from baseline (IQR)	22 (8-45)	9 (0-27)	.001
Only patients with preoperative GFR <60 mL/min (No. of pts)	13	20	
Median % Cr increase from baseline (IQR)	40 (7-57)	9 (−5 to 28)	.04

AKI, Acute kidney injury; *AKIN*, Acute Kidney Injury Network; *HD*, hemodialysis; *Cr*, creatinine; *IQR*, interquartile range; *GFR*, glomerular filtration rate; *pts*, patients.

Magruder et al. also mentioned several limitations to their study. The lack of randomization, inability to assess individual goals as they had a bundled goal directive approach, and many patients receiving GDP had normal renal function and therefore stood to benefit little from practices that may show a larger effect in those with a higher preoperative probability of developing cardiac surgery associated AKI. Their conclusions state that the use of GDP overall were associated with lower incidence of AKI and milder increases in serum creatinine as compared to their control group. Magruder et al stated that to

assess the effect of such measures in patients at greatest risk for cardiac surgery associated AKI, more studies using GDP should be directed towards older patients who present with impaired renal function.

Methodology

The study design consisted of a prospective observational pilot study conducted during two months of activity in the cardiac surgery department of our institution. In total 19 patients were included in the study. Five patients were excluded from the study because they were scheduled for LVAD implants. All monitoring equipment and standard of care practices were used for all patients according to facility policies, in addition to the renal oximetry sensors. Both cerebral and renal oximetry sensors were placed and a baseline reading was obtained prior to anesthesia induction and intubation. This was done to achieve the most accurate baseline before metabolic demands were influenced. Renal sensors were placed based upon 11th and 12th intercostal space and posterior for both left and right flank positions. Baseline and preoperative values were obtained: Age, weight, height, BSA, diabetic, EF, creatinine, hemoglobin (hgb) and hematocrit (hct), cerebral and renal oximetry values, and lactate. These parameters were collected based upon evidence based practice that several of these parameters are statistically significant towards AKI outcomes (31). Every 15 minutes upon initiation of CPB the following variables are recorded: Hgb, MAP, pump flow, pump CI, cerebral oximetry, renal oximetry, lactate, temperature (bladder), oxygen delivery, and SVO2. The range of temperature in this group was between 28-34.4C.

Oxygen delivery was calculated using: *DO2=pump flow index x (hemoglobin x 1.36 x hemoglobin saturation + 0.003 x arterial oxygen tension) x 10* (30). A further abbreviated formula can be calculated using: *DO2= 13.4 x HBG x CI* achieving the same oxygen delivery amount in mL/min1/m2, assuming 100% FiO2. Any patient that was under the nadir oxygen delivery of 272 mL/min1/m2 as published by the Ranucci group during CPB, then the percent of time under that level will be evaluate towards AKI outcomes. Continuous CDI monitoring was also used and calibrated accordingly. CDI is a continuous

blood parameter monitoring system for improved blood gas management. A sensor is placed in line with the CPB circuit, blood flows past the sterile micro sensor where accurate measurements are displayed on the monitor. CDI monitors arterial and venous blood gas parameters: pH, pCO2, pO2, potassium, bicarbonate, temperature, base excess, SO2, flow, HGB and HCT. With every blood gas drawn for lab analysis, the CDI machine values were stored and updated to reflect the most accurate analysis. At the end of the case the CPB duration, cross clamp duration, total urine output, and any RBC received was recorded. Postoperatively the BUN, Creatinine, EGFR and lactate levels were recorded up to 48 hours postop. Creatinine is freely filtered across the glomerulus and is neither reabsorbed nor metabolized by the kidney (although tubular secretion does occur), it serves as a marker of renal function in clinical practice. However, serum creatinine does have some important limitations it can take 24–36 hours to rise after a definite renal insult (1). For that reason the collection of serum creatinine levels were carried out to the 48 hour post-surgery mark.

Hypothesis and Specific Aims

The primary goal was to correlate the renal oximetry values to already established markers that are routinely measured during CPB (HGB, Cerebral Oximetry, MAP, CI, Temp, SVO2, and DO2). We hypothesized that changes in these markers will correlate with changes in renal oximetry values. Secondly, we hypothesized that changes in adult renal oximetry will correlate with changes in oxygen delivery during CPB. In this way, the INVOS™ device could provide a real time trending device to reduce the incidence of AKI. Lastly, we investigated the use of pulsatile vs. non-pulsatile flow. We hypothesize that pulsatile flow will be superior to non-pulsatile flow and have better outcomes on patient's post-operative creatinine levels.

Statistical Analysis

Baseline pre-operative and operative characteristics, were gathered for all participants and patients were grouped based upon surgery type: AVR/MVR and CABG. For all parameters mean ±

standard deviation were calculated. A p-value to evaluate the significance between the surgical groups was derived from two-sample t test with unequal variances for continuous variables and Fisher's exact test for categorical variables. A p-value of less than 0.05 will be used to determine strong significance. The use of pulsatile flow vs. non-pulsatile flow patients were also recorded. Post-operative results based on changes from pre-operative levels were recorded in regards to BUN, Creatinine, and Lactate. These changes were analyzed using mean change from the baseline level ± standard deviation based on the aggregated data. Sub-groups compared were: pulsatile vs. non-pulsatile, AKI vs. no AKI, AVR/MVR vs. CABG. This was derived from a linear mixed effects model with a random intercept accounting for within subject dependence. This is similar to a paired t-test to evaluate whether the mean change is significantly different from zero. The same was done to also quantify the percent change from baseline. The same analysis was also run to assess the frequency of patients with at least one value > 20% change from the baseline level and the p-values were derived from a Fisher's exact test.

The total population (N=19) with sub-groups associated with post-op results (changes from pre-operative) based on all participants included these variables: BUN, Creatinine, and Lactate. Operative values included were: RBC given, Lowest DO2, Percent of DO2<272, Lowest HGB, and Lowest temperature. The p-values for significance were obtained by regression coefficient ± standard error derived from a linear mixed effects model with a random intercept to account for within-subject correlation. The same analysis was run with the total number of patients with no AKI, i.e. healthy renal function (n=13). The same analysis was also run for the total number of patients with known AKI prior to surgery (n=6).

Any patient that received a red blood cell transfusion (N=4), the renal oximetry values were recorded before and after RBC administration. Values were recorded mean ± standard deviation based on the aggregated data with p-values derived from a linear mixed effects model with a random intercept to account for within-subject correlation. Based upon Ranucci et al. findings of oxygen delivery and AKI

correlation, to use flank oximetry there needs to be an identification of variables associated with renal oximetry values (both left and right). Specifically these targeted variables are: HGB, Cerebral oximetry (left and right), MAP, CI, Temperature, SVO2, and DO2. The significance was determined by a regression coefficient ± standard error derived from a linear mixed effects model with a random intercept to account for within-subject correlation. Due to the fact the INVOS™ NIRS monitoring system was used, and published adult data has shown that an rSO2 of 20% decline from baseline are cause for concern and intervention, and an rSO2 of 25% decline from baseline are associated with neurologic dysfunction and adverse outcomes (32). For that reason a relationship between DO2 (dependent variable) and % changes in Renal saturation from pre-operative (independent variable) was a necessary evaluation. Percent change in left and right renal values were recorded as well as a decrease more than 20% in left and right renal saturations. The percent changes were derived from a regression coefficient ± standard error derived from a linear mixed effects model with a random intercept. The p-values for significance were derived from a correlation coefficient between DO2 and Renal Number based on a linear mixed effects model with a random intercept. The importance of separating the Left and Right renal oximetry values is due to the physiology and differences in renal blood flow. The left kidney renal vein is slightly longer than the right which can account for differences in blood flow (40). Tarzamni et al. designed a study to investigate anatomical differences in the right and left renal arterial patterns. The results concluded there was no significant difference in diameter between the left and right renal arteries or in the distance to branching ($p = 0.35$; $p = 0.11$). An accessory artery was presented in 58 of 117 kidneys and this significantly more often occurred on the right kidney than on the left ($p = 0.01$) (38).

Results

The overall descriptive characteristics of the patients are listed in Table 1 grouped according to type of surgery.

Table 3: Characteristics of the study participants (N=19)

Variables	All (N=19)	MVR/AVR (N=7)	CABG (N=12)	p-value[b]
Pre-operative				
Age	60.26±13.65[a]	59.71±19.01	60.58±10.38	0.91
Weight (kg)	84.14±14.26	89.39±11.08	81.08±15.43	0.19
Height (cm)	169.39±9.22	169.47±7.44	169.34±10.44	0.98
BSA	1.98±0.20	2.05±0.15	1.94±0.22	0.25
EF (%)	55.58±10.91	56.00±12.30	55.33±10.58	0.91
CPB	144.47±38.82	157.71±47.47	136.75±32.57	0.33
XC	102.63±34.54	116.57±40.36	94.50±29.47	0.24
Pulsatile (>0)	13 (68.42%)	6 (85.71%)	7 (58.33%)	0.33
Pulsatile[c]	113.92±35.20	125.00±36.86	104.43±33.45	0.32
UOP	290.26±201.23	274.29±138.16	299.58±235.78	0.77
HGB	11.63±1.61	11.83±2.09	11.52±1.35	0.73
BUN	19.53±13.01	19.29±7.18	19.67±15.77	0.94
Creatinine	1.87±2.56	1.10±0.37	2.33±3.18	0.21
Creatinine (>1.2)	7 (36.84%)	3 (42.86%)	4 (33.33%)	1.00
eGFR (>60)	14 (73.68%)	5 (71.43%)	9 (75.00%)	1.00
Lactate	1.08±0.57	1.09±0.39	1.08±0.67	0.97
Cerebral sat #1	61.58±10.04	64.43±12.74	59.92±8.25	0.42
Cerebral sat #2	61.58±10.28	64.29±13.03	60.00±8.53	0.46
Renal sat #1	73.84±11.33	73.71±12.12	73.92±11.40	0.97
Renal sat #2	73.63±10.63	76.43±11.40	72.00±10.30	0.41
Kidney disease	6 (31.58%)	2 (28.57%)	4 (33.33%)	1.00
Operative				
RBC	4 (21.05%)	1 (14.29%)	3 (25.00%)	1.00
Lowest DO2	228.53±34.88	230.43±31.90	227.43±37.84	0.86
% of DO2<272	63.51%±38.47%	53.18±36.92	69.54±39.63	0.38
Lowest HGB	8.27±1.27	8.51±1.05	8.13±1.41	0.50
Lowest Temp	32.17±1.46	31.79±2.26	32.40±0.74	0.51

[a]mean±standard deviation

[b]derived from two-sample t test with unequal variances for continuous variables and Fisher's exact test for categorical variables

[c]only based on subjects with pulsatile value >0

There was no statistical difference between the AVR/MVR and the CABG patient cohorts in terms of pre-operative and operative parameters listed in Table 3.

Table 4A: Post-op results up to 48 hours (changes from pre-operative)

Variable	**BUN** 0.85±3.34[a] (p=0.24[b])	**Creatinine** -0.09±0.68 (p=0.58)	**Lactate** **0.40±0.41 (p<0.001)**
Pulsatile			
Non-pulsatile (N=6)	0.38±3.78 (p=0.75)	0.12±0.16 (p=0.09)	0.52±0.65 (p=0.09)
Pulsatile (N=13)	1.06±3.25 (p=0.25)	-0.19±0.81 (p=0.43)	**0.34±0.25 (p<0.001)**
p-value	0.68	0.20	0.60
Renal dysfunction			
No (N=13)	0.30±2.15 (p=0.57)	-0.03±0.16 (p=0.54)	**0.33±0.34 (p<0.01)**
Yes (N=6)	2.03±5.15 (p=0.31)	-0.23±1.26 (p=0.66)	**0.53±0.54 (p<0.05)**
p-value	0.35	0.69	0.46
CABG			
No (N=7)	-0.52±2.96 (p=0.61)	-0.01±0.20 (p=0.86)	**0.45±0.45 (p=0.01)**
Yes (N=12)	1.64±3.40 (p=0.13)	-0.14±0.85 (p=0.59)	**0.36±0.40 (p=0.01)**
p-value	0.12	0.63	0.69

[a]mean change from the baseline level ± standard deviation based on the aggregated data

[b]derived from a linear mixed effects model with a random intercept accounting for within subject dependence. This is similar to a pair t test to evaluate whether the mean change is significantly different from zero.

Table 4 shows the changes from pre-operative based upon the changes in baseline from BUN, Creatinine and Lactate. The total group was analyzed in three subcategories: Pulsatile vs. non-pulsatile, AKI vs. no AKI, and AVR/MVR vs. CABG. The only variable that shows any statistical significance is the changes in lactate. However only individually, and they were not significant when compared within each sub-group. Table 4b below shows greater than 20% increase in changes from post-operative values. This approach was taken, because some investigations have reported that even mild changes in renal function are associated with worse outcomes (27). The only p-value of significance was the creatinine in the pulsatile vs. non-pulsatile group. The difference between the two groups were significant when it came to increases in creatinine, $p < 0.05$. In the non-pulsatile group 4 out of 6 patients had a greater than 20% increase from baseline in serum creatinine; whereas 2 out of 13 patients in the pulsatile group had an increase of greater than 20% from baseline. The difference between pulsatile and non-pulsatile were statistically significant.

Table 4b: Post-op results up to 48 hours (frequency of >20% changes from pre-operative)

Variable	**BUN** 10[a] (52.63%)	**Creatinine** 6 (31.58%)
Pulsatile		
Non-pulsatile (N=6)	4 (66.67%)	4 (66.67%)
Pulsatile (N=13)	6 (46.15%)	2 (15.38%)
p-value	0.63[b]	**<0.05**
Renal dysfunction		
No (N=13)	7 (53.85%)	3 (23.08%)
Yes (N=6)	3 (50.00%)	3 (50.00%)
p-value	1.00	0.32
CABG		
No (N=7)	2 (28.57%)	2 (28.57%)
Yes (N=12)	8 (66.67%)	4 (33.33%)
p-value	0.17	1.00

[a]frequency of patients with at least one > 20% change from the baseline level
[b]derived from a Fisher's exact test

The next subset will distinguish between all parameters within the group together, as well as separating out AKI patients and examining any differences. Table 5A has all of the subjects (N=19) grouped together. Ejection fraction had a negative correlation with the changes in BUN, p=0.04. So the higher the baseline EF%, the lower the changes in BUN as compared with someone with a lower baseline EF%. There was a negative correlation between lactate and BUN levels, p=0.02. The higher the baseline lactate pre-operatively; the lower the BUN changes between a patient with a lower starting lactate. Lower starting BUN and Creatinine baselines, had lower changes in BUN and Creatinine as compared to higher starting values (p<0.0001 for both). Lower baseline creatinine levels were also associated with lower changes in lactate as compared to higher starting creatinine (p=0.04).

Table 5A: Identification of variables associated with post-op results (changes from pre-operative) based on all participants (N=19)

Variable	Changes in BUN	Changes in creatinine	Changes in lactate
Pre-operative			
Age	0.02±0.05; p=0.60[a]	0.01±0.01; p=0.21	0.002±0.007; p=0.74
Weight (kg)	0.01±0.05; p=0.81	-0.001±0.006; p=0.88	-0.006±0.006; p=0.34
Height (cm)	0.06±0.07; p=0.40	0.0004±0.017; p=0.98	-0.01±0.01; p=0.26
BSA	1.28±3.42; p=0.71	-0.05±0.56; p=0.92	-0.39±0.48; p=0.42
EF (%)	**-9.91±4.68; p=0.04**	0.37±0.84; p=0.67	-0.52±0.49; p=0.29
CPB	-0.02±0.02; p=0.34	-0.004±0.002; p=0.13	-0.001±0.002; p=0.59
XC	-0.03±0.02; p=0.21	*-0.006±0.003; p=0.08*	-0.001±0.003; p=0.62
Pulsatile (>0)	0.73±1.74; p=0.68	-0.30±0.23; p=0.20	-0.13±0.25; p=0.60
UOP	-0.002±0.004; p=0.58	0.0003±0.0010; p=0.79	0.0004±0.0004; p=0.24
HGB	-0.28≥0.55; p=0.61	0.09±0.11; p=0.42	0.07±0.05; p=0.15
BUN	-0.05±0.03; p=0.11	**0.030±0.007; p<0.0001**	-0.008±0.006; p=0.18
Creatinine	0.17±0.10; p=0.10	**0.21±0.02; p<0.0001**	**0.05±0.02; p=0.04**
Lactate	**-2.57±1.11; p=0.02**	-0.35±0.25; p=0.17	**-0.27±0.12; p=0.02**
Kidney disease	2.08±2.19; p=0.35	-0.19±0.48; p=0.69	0.15±0.20; p=0.46
CABG	2.33±1.46; p=0.12	-0.12±0.25; p=0.63	-0.07±0.18; p=0.69
Operative			
RBC	2.48±2.57; p=0.34	0.10±0.59; p=0.87	0.11±0.13; p=0.40
Lowest DO2	0.003±0.012; p=0.78	0.004±0.003; p=0.16	-0.003±0.002; p=0.10
% of DO2<272	1.56±1.93; p=0.42	0.09±0.33; p=0.78	0.25±0.19; p=0.20
Lowest HGB	0.16±0.55; p=0.78	0.13±0.13; p=0.33	-0.03±0.05; p=0.53
Lowest Temp	0.69±0.41; p=0.10	0.11±0.07; p=0.14	0.003±0.042; p=0.94

[a]regression coefficient±standard error derived from a linear mixed effects model with a random intercept to account for within-subject correlation

In this group is when we begin to see the effects of pulsatile flow vs. non-pulsatile flow in terms of creatinine. The pulsatile group (p=0.02) had a negative correlation and showed lower changes in creatinine as compared to the non-pulsatile cohort. Urine output (UOP) was also statistically significant (p=0.03). The more urine output during CPB was correlated with lower changes in creatinine levels. The higher the baseline EF then the lower the changes in creatinine (p=0.02). The longer the XC time during surgery the higher the changes in BUN and Creatinine post-operatively (p=0.04, p=0.01).

All of the operative correlations relate to changes in BUN. The lowest nadir DO2 on CPB was significant to higher changes in BUN (p=0.03). Since the Ranucci group defined the lower limit of DO2

and AKI outcomes at 272 mL/min1/m2, we examined the percent of time under that mark to determine any associated outcomes at our institution. The greater the time under a DO2 of 272 mL/min1/m2, the greater the changes in BUN (p=0.03).

Table 5B: Identification of variables associated with post-op results (changes from pre-operative) based on participants with no renal dysfunction (N=13)

Variable	**Changes in BUN**	**Changes in creatinine**	**Changes in lactate**
Pre-operative			
Age	0.03±0.03; p=0.28	0.001±0.003; p=0.59	-0.007±0.007; p=0.35
Weight (kg)	0.01±0.04; p=0.81	-0.001±0.003; p=0.80	-0.006±0.006; p=0.36
Height (cm)	**0.09±0.04; p=0.03**	**0.005±0.002; p=0.02**	-0.01±0.01; p=0.42
BSA	1.18±2.48; p=0.64	-0.02±0.19; p=0.92	-0.34±0.48; p=0.48
EF (%)	-8.85±6.07; p=0.15	**-0.81±0.32; p=0.02**	-0.48±0.55; p=0.39
CPB	0.01±0.01; p=0.19	0.001±0.001; p=0.14	0.0004±0.0022; p=0.84
XC	**0.02±0.01; p=0.04**	**0.002±0.001; p=0.01**	0.0006±0.0026; p=0.83
Pulsatile (>0)	-1.80±1.36; p=0.19	**-0.18±0.07; p=0.02**	-0.01±0.23; p=0.98
UOP	-0.000±0.002; p=0.90	**-0.0004±0.0002; p=0.03**	**0.0007±0.0003; p=0.02**
HGB	0.17±0.28; p=0.53	0.01±0.03; p=0.68	0.01±0.05; p=0.78
BUN	-0.12±0.08; p=0.13	-0.004±0.009; p=0.70	-0.02±0.02; p=0.15
Creatinine	5.98±4.73; p=0.21	0.18±0.30; p=0.56	0.38±0.54; p=0.48
Lactate	**-1.76±0.82; p=0.04**	-0.02±0.06; p=0.69	*-0.28±0.14; p=0.06*
Operative			
RBC	-0.01±0.69; p=0.98	-0.11±0.09; p=0.27	0.18±0.18; p=0.33
Lowest DO2	**-0.02±0.01; p=0.03**	-0.0014±0.0008; p=0.11	*-0.004±0.002; p=0.08*
% of DO2<272	**1.71±0.76; p=0.03**	0.10±0.10; p=0.32	0.34±0.26; p=0.20
Lowest HGB	**0.65±0.29; p=0.03**	0.04±0.03; p=0.19	-0.09±0.06; p=0.18
Lowest Temp	0.39±0.24; p=0.11	0.03±0.02; p=0.13	-0.04±0.03; p=0.30

[a]regression coefficient±standard error derived from a linear mixed effects model with a random intercept to account for within-subject correlation

Table 5C is the group of patients coming into surgery with known AKI or some type of renal insult. There was a total of N=6.

Table 5C: Identification of variables associated with post-op results (changes from pre-operative) based on participants with known renal insult (N=6)

Variable	Changes in BUN	Changes in creatinine	Changes in lactate
Pre-operative			
Age	-0.02±0.14; p=0.86	**0.04±0.01; p<0.01**	0.02±0.01; p=0.14
Weight (kg)	-0.04±0.16; p=0.82	0.00±0.04;p=0.99	-0.008±0.014; p=0.58
Height (cm)	-0.07±0.17; p=0.68	-0.01±0.05; p=0.83	-0.02±0.02; p=0.35
BSA	-2.55±11.86; p=0.83	-0.04±3.04; p=0.99	-0.82±1.17; p=0.49
EF (%)	-5.98±27.65; p=0.83	-4.32±5.03; p=0.40	0.67±2.62; p=0.80
CPB	0.01±0.14; p=0.94	**0.04±0.02; p=0.04**	**0.020±0.008; p=0.03**
XC	-0.02±0.13; p=0.86	**0.04±0.02; p=0.02**	*0.017±0.009; p=0.07*
Pulsatile (>0)	**8.64±2.04; p<0.001**	-0.62±0.56; p=0.28	**-1.05±0.15; p<0.0001**
UOP	0.007±0.011; p=0.56	0.002±0.003; p=0.47	0.001±0.001; p=0.18
HGB	-0.76±1.15; p=0.52	0.20±0.23; p=0.40	**-0.17±0.08; p=0.04**
BUN	*-0.15±0.08; p=0.07*	**-0.05±0.01; p<0.001**	**-0.017±0.003; p<0.0001**
Creatinine	0.61±0.37; p=0.11	**0.27±0.06; p<0.001**	**0.09±0.02; p<0.0001**
Lactate	-3.54±2.01; p=0.09	**-1.39±0.47; p<0.01**	-0.22±0.14; p=0.14
CABG	1.56±0.97; p=0.12	0.12±0.08; p=0.12	0.16±0.16; p=0.33
Operative			
RBC	3.83±4.17; p=0.37	0.47±1.18; p=0.70	-0.07±0.28; p=0.81
Lowest DO2	-0.03±0.11; p=0.81	**-0.03±0.01; p<0.01**	0.012±0.009; p=0.17
% of DO2<272	**24.62±5.20; p<0.001**	1.05±2.16; p=0.63	**1.47±0.72; p=0.05 ***
Lowest HGB	-1.25±2.02; p=0.54	-0.36±0.27; p=0.20	0.26±0.15; p=0.10
Lowest Temp	4.24±3.33; p=0.22	**2.11±0.33; p<0.0001**	**0.62±0.26; p=0.03**

[a]regression coefficient±standard error derived from a linear mixed effects model with a random intercept to account for within-subject correlation

There are some differences amongst the AKI group and the non AKI group. Age was a significant factor with changes in creatinine (p<0.01). CPB times were statistically significant for changes in creatinine for AKI group compared to the non AKI group (p<0.001). The longer the CPB time, the greater the changes in creatinine and lactate (p=0.04, p=0.03). The longer the XC time the greater the changes in creatinine (p=0.02). The lowest nadir DO2 had a strong correlation with changes in creatinine (p<0.01). The lower the nadir DO2 the higher the changes in creatinine. The % of DO2 under 272 mL/min1/m2 also correlated with increasing BUN and increasing lactates (p<0.001, p=0.05). Lowest temperature played a role in changes in both creatinine and lactates. The lower the coldest bladder

temperature, the lower the changes in creatinine and lactates for the AKI group (p<0.0001, p=0.03). The coldest temperature ranges were between 28-34.2 C.

Table 6: Changes in renal oximetry when blood is given based on the 4 participants receiving RBC

Time	Left Renal	Right Renal
Before RBC	64.21±17.52[a]	65.65±16.37
After RBC	68.53±12.58	67.60±12.75
p-value[b]	*0.08*	0.18

[a]mean±standard deviation based on the aggregated data

[b]derived from a linear mixed effects model with a random intercept to account for within-subject correlation

Table 6 shows the changes in renal oximetry values when red blood cells were given. Only 4 patients received any RBC out of the 19 (21%). However, 3 out of the 4 patients were in the AKI group with pre-existing renal insults. RBC's were given at the surgeon's discretion or bypass parameters were indications to give based upon institutional protocol. The transfusion trigger was multifactorial.

Table 7: Identification of variables associated with renal oximetry
Mean Change in Response Variable for One Unit of Change in Predictor Variable

Predictor Variables	Left Renal (Response Variable %)	Right Renal (Response Varible %)	Predictor Variable Range
HGB	**5.57±1.77; p<0.01**[a]	**5.14±1.90; p=0.01**	7 - 13.24 g/dL
Cerebral Number 1 & 2	0.14±0.26; p=0.58	0.23±0.31; p=0.46	34 – 87 %
MAP	0.19±0.13; p=0.15	0.18±0.16; p=0.25	40 – 125 mmHg
CI	**15.90±2.59; p<0.0001**	**13.82±5.06; p<0.01**	1.44 – 2.79 L/min/m2
Temp (C)	**-2.16±0.91; p=0.02**	*-1.95±1.04; p=0.07*	28 – 34.2 C
SVO2	0.08±0.20; p=0.68	0.12±0.23; p=0.61	60 – 90 %
DO2	**0.17±0.02; p<0.0001**	**0.17±0.04; p<0.0001**	193.35 – 369 ml/min1/m2

[a]regression coefficient±standard error derived from a linear mixed effects model with a random intercept to account for within-subject correlation

Table 7 shows different operative variables associated with the renal oximetry saturation values. These parameters are how we assess and evaluate the adequacy of perfusion for each individual CPB surgery. With a small (n=19) sample size there are strong correlations between variables being monitored routinely during CPB. The higher the HGB values the higher the renal saturations for both left and right oximetry values (p<0.01, p=0.01). The Cerebral oximetry numbers did not correlate with

the renal values; due to its already documented sensitivity to CO2 levels and cerebral vasodilatory effects. There have been many studies documenting the importance of a mean arterial pressure for cerebral and renal perfusion (36). The higher the MAP the higher both renal oximetry values, however this was not statistically significant. Cardiac Index also had a strong correlation with the renal oximetry saturations. The higher the CI values the higher the renal saturations ($p<0.0001$, $p<0.01$). Temperature also was statistically significant. However in just the left oximetry saturations but not the right ($p=0.02$, $p=0.07$). This is still biologically significant. With a lower temperature the renal values are much higher, due to decreased metabolism and decreased O2 consumption. And likewise with warmer temperatures there are lower renal oximetry saturations from an increase metabolism and increased oxygen consumption. Venous oxygen saturation values did not correlate with the oximetry values. The strongest correlation of all the parameters was the oxygen delivery. The DO2 had significance of $p<0.0001$ and $p<0.0001$ for both left and right renal NIRS.

Table 8 accounts for percent changes in renal values as well as decreases of more than 20% from baseline and comparing corresponding DO2. The decrease of 20% approach was investigated due to the INVOS™ company recommending that a decrease of 20% or greater from baseline implies the need for an intervention.

Table 8: Relationship between DO2 (dependent variable) and % changes in Renal sat from pre-operative (independent variable)

Variables	**DO2 (dependent variable) ml/min1/m2**
1 % change in Left Renal	**1.15±0.35[a]; p<0.01**;
1 % change in Right Renal	**0.94±0.33; p<0.01**;
Decrease more than 20% in Left Renal	**-21.97±8.86; p=0.01**
Decrease more than 20% in Right Renal	*-17.83±9.55; p=0.06*

[a] regression coefficient ± standard error derived a linear mixed effects model with a random intercept

[b] correlation coefficient between DO2 and Renal Number based on a linear mixed effects model with a random intercept

There is a significant positive correlation between DO2 levels and percent changes in renal oximetry.

Specifically as the DO2 increases 1.15 mL/min1/m2 ($p<0.01$), the percent change in the left renal oximetry increases 1%. The same is true for the right renal values. As the DO2 increases 0.94 mL/min1/m2 ($p<0.01$), the percent change in the right oximetry increases 1%. The left renal oximetry with a decrease of more than 20% from pre-operative baseline is associated with a significantly lower DO2 than left renal oximetry values without a decrease more than 20% from pre-operative ($p=0.01$). The DO2 of this decrease renal saturation group was found to have a difference of 21.97 ml/min1/m2. The same is true for decreases more than 20% for right renal oximetry values, however the p-value is slightly above significance. We believe with a larger sample size this correlation could be proven to a higher degree.

Discussion

Interventions to prevent or reduce incidences of AKI during CPB are a necessity for the greatest impact on a patient's clinical trajectory and outcomes. Through this prospective pilot study, the evidence provided has shown statistical correlations towards changes in oxygen delivery, changes in renal oximetry, and changes in patient's BUN and Creatinine levels impacting AKI outcomes.

Table 3 shows the descriptive statistics of the patient population. They are shown as a total, as well as separated out as MVR/AVR vs. CABG. There was not any statistical differences amongst all the parameters in the groups. As a national standard there should not be a difference amongst the two groups, even though the biological ischemic disease process is different between them.

Healthy Kidney vs Prior AKI Group

In tables 5, 5b, & 5C statistical significance was achieved in parameters that have been previously published towards AKI outcomes. Data suggests that a higher EF% the better the kidney outcomes. We found the same endpoints, with higher EF% values the less changes in creatinine post-operatively. Also the longer the CPB times and XC times, the higher the changes in BUN and Creatinine post-operatively. However, the difference between healthy kidney patients and AKI patients before

surgery was very evident. The XC time was statistically significant for BUN and Creatinine in the healthy renal group. The longer the XC time the higher the BUN and Creatinine levels post-op as compared to shorter XC times (p=0.04, p=0.01). However the CPB times were not significant in this group. In the AKI cohort, the XC and CPB times were directly correlated with increases in creatinine (p=0.04, p=0.02). Urine output had correlations with the healthy renal group and not for the AKI group. The minimum acceptable amount of urine produced during CPB has been defined as >1ml/kg/hr (26). The more urine that was produced during CPB the less changes in creatinine (p=0.03). It must be stated, at this institution the use of mannitol during CPB is part of the standard of care. All patients received a dose between 25g-37.5g total, in 12.5g bolus increments. This is in comparison to the Johns Hopkins GDP study that restricted mannitol use. It has been shown in research that mannitol: 1) induces an osmotic diuresis which prevents tubular obstruction; 2) decrease the epithelial and endothelial cell swelling limiting the vascular congestion and tubular obstruction; 3) is a free radical scavenger; 4) increases the synthesis of intra-renal prostaglandin generating an efficacious renal vasodilation (9). Although there are pharmacological reports with mannitol, there are also conflicting data on its use during CPB for renal perfusion. Magruder et. al with John Hopkins sought to minimize mannitol use because of its unproven benefits, and it can mask real-time urine output as a marker for renal perfusion. However 17% of their patients still received mannitol (27). There is not a control group that did not receive any mannitol at all in this pilot study. So urine output should not be masked, since all patients received similar dosing.

All the variables associated with statistical change in the healthy kidney cohort were in the changes in BUN levels. Lower DO2 levels were associated with higher changes in BUN (p=0.03) and an increased % of time under DO2 of 272 ml/min/m2 were associated with higher changes in BUN (p=0.03) Increasing this BUN:Creatinine ratio could be indicative of a pre-renal insult, which is shown by the DO2 variables. By increasing the pump flow index (cardiac output), you are increasing the oxygen delivery and minimizing time under 272 ml/min/m2 thus decreasing the changes in BUN levels post-operatively.

This supports adjusting pump parameters to minimize pre-renal azotemia and further developing kidney insults. In comparison, the AKI group operative variables were associated with both changes in BUN and Creatinine. The Lowest DO2 was directly correlated with changes in Creatinine ($p<0.01$), which is different from the healthy kidney group. The lower the DO2 level the higher the increase in creatinine post-operatively. The % of time under DO2 of 272 ml/min/m2 was similar and correlated to changes in BUN. The higher the time under 272ml/min/m2, the higher the changes in BUN levels. However, this also correlated with changes in lactate levels ($p=0.05$). The higher the time under 272 ml/min/m2 the higher the lactate levels indicating worse ischemia and higher anaerobic metabolism. Temperature correlated with the AKI group in changes in creatinine and lactates ($p<0.0001$, $p=0.03$). This was not true in the healthy kidney cohort. The lower the lowest temperature, the lower the changes in creatinine and lactate levels. This is showing a drastic difference in this high risk AKI group vs. the healthy kidney group. If you decrease the core temperature on these high risk patients with less of a reserve compared to the healthy group, then statistically shown you can decrease post-operative creatinine and lactate levels. However, this cooling process and rewarming cannot be at the expense of creating longer CPB times, which are shown to increase post-op BUN and Creatinine levels. The statistical evidence is pointing towards an increased need for this high risk group, to have higher DO2 and the renal benefit of colder temperatures, not at the expense of longer CPB times. These outcomes support Magruder et al.'s findings that further research is needed to assess the measures in patients at greatest risk for cardiac surgery associated AKI: older patients who present with impaired renal function.

HGB, CI, & DO2

Table 7 & 8 directly support our hypothesis and specific aims of the pilot study. Table 7 statistically correlates changes in perfusion parameters with changes in renal oximetry. Hemoglobin, cardiac index, and oxygen delivery all had strong statistical correlations with both left and right renal

values. The correlation between HGB and CI further strengthen the relationship between DO2 and renal oximetry. They are two of the variables that are calculated in the equation for DO2 (10).

DO2=pump flow index x (hgb x 1.36 x hgb saturation + 0.003 x arterial oxygen tension) x 10.

According to Table 7, the range of HGB of these patients were between 7-13.24 g/dL. For every increase in HGB value, the mean change in the left was increased 5.57% and right renal oximetry 5.14% ($p<0.01$, $p=0.01$). This quantifies the changes in HGB values to changes in renal oximetry variables. The same holds true for CI values. With a range of 1.44-2.79 L/min/ m2, for every increase in CI the mean change in left renal oximetry was 15.9% and right renal oximetry was 13.82% respectively ($p<0.0001$, $p<0.01$). The changes in DO2 were also strongly reflected in the changes in left and right renal oximetry values ($p<0.0001$, $p<0.0001$)

In Table 8 the specific changes in renal oximetry values and DO2 were identified. As the DO2 increases 1.15 mL/min/m2 ($p<0.01$) the percent change in the left renal oximetry increases 1%; in correlation as the DO2 increases 0.94 mL/min/m2 ($p<0.01$) the percent change in the right oximetry increases 1%. Since we identified the exact changes in oxygen delivery, the INVOS™ company recommends that a decrease of 20% or greater from baseline implies the need for an intervention. The data shows the left renal oximetry with a decrease of more than 20% from pre-operative baseline is associated with a significantly lower DO2 than left renal oximetry values without a decrease more than 20% from pre-operative ($p=0.01$). The difference between patients with a 20% decrease and patients without was quantified at 21.97 ml/min1/m2. So recommendations to increase pump flow to achieve greater than 21.97 ml/min/m2 difference in DO2 are indicated to increase renal oximetry saturations. The same is true for the right renal oximetry values however the p-value again was slightly above significant ($p=0.06$). Tarzamni et al.'s group looked for anatomical differences amongst right and left kidney arterial patterns. They found no significant difference in diameter between the left and right renal arteries or in the distance to branching. However an accessory artery was present and this

significantly more often occurred on the right side than on the left (p=0.01). This could help explain why the right renal oximetry p-values slightly lag behind the left, when correlating to perfusion parameters and oxygen delivery. This extra accessory artery could be an extra shunt thus affecting blood flow and oxygen delivery to the right kidney.

Pulsatile Flow

In Table 4 we examined the difference between non-pulsatile and pulsatile flow. Pulsatility generated less of an increase in lactate production as compared to non-pulsatile flow ($p<0.001$). Lower lactate increases are indications of adequacy of perfusion and less anaerobic metabolism as compared to a higher lactate production. The use of pulsatility has shown benefits of increasing microvascular perfusion thus limiting the amount of lactate produced from anaerobic metabolism. The non-pulsatile group on average had a net increase in serum creatinine as compared to pulsatile flow which had a net decrease in creatinine. However the difference in the two were not significant (p=0.2). Table 4b shows the number of patients who had an increase of 20% or greater from baseline in creatinine. Non-pulsatile had 66.7% of patients with this increase compared to 15.3% in the pulsatile group. The difference between the two was significant ($p<0.05$) indicating the superiority of the pulsatile group amongst patients trending towards AKI stage 1. Pulsatile flow in the healthy kidney group had the strongest correlation with lower creatinine levels post-op (p=0.02) as compared to the AKI group with the strongest correlation to lower BUN levels ($p<0.001$). The use of pulsatile flow has shown to have more positive outcomes for both BUN and creatinine levels as compared to non-pulsatile leading to better patient clinical trajectories.

CONCLUSION

Zarbock et al. stated that a reliable means to prevent acute kidney injury remains elusive. Through evidence based practice from the Ranucci et al. data and Magruder et al. study; we have learned parameters that influence and affect AKI and renal outcomes. For the adult population there

has not been a real-time monitoring device, trending the risk of developing AKI during CPB surgery. From data extrapolated from this pilot study, we can statistically correlate the changes in perfusion parameters (HGB, CI, TEMP, DO2) during CPB to changes in both right and left renal oximetry saturation values. As well as defined an exact change in oxygen delivery with exact changes in renal oximetry saturation values. Even though the distance from sensor to organ is greater than in pediatrics, this pilot study proves the use of the INVOS™ Cerebral/Somatic oximetry machine to be a valuable real time trending device during intra-operative CPB to help reduce AKI outcomes. Pulsatile flow also proved to be superior to non-pulsatile in terms of postoperative BUN, Creatinine, and Lactate levels.

Future directions should include randomized control trials. We have shown a difference between healthy kidney patients and known renal insult patients prior to CPB surgery and the need for higher DO2 were more evident in the high risk renal group. The need for more studies including high risk patients with renal insults for CPB studies is evident and they require different perfusion strategies compared to healthy renal patients.

References

1. Adademir, T., Ak, K., Aljodi, M., Elçi, M. E., Arsan, S., & Selim, I. (2012). The effects of pulsatile cardiopulmonary bypass on acute kidney injury, 35, 511–519. http://doi.org/10.5301/ijao.5000097

2. Aĝirbaşli, M. a, Song, J., Lei, F., Wang, S., Kunselman, A. R., Clark, J. B., … Ündar, A. (2014). Comparative effects of pulsatile and nonpulsatile flow on plasma fibrinolytic balance in pediatric patients undergoing cardiopulmonary bypass. Artificial Organs, 38(1), 28–33. http://doi.org/10.1111/aor.12182

3. Alexander HC, Kronenefeld MA, Dance GR. Reduced postoperative length of stay may result from using cerebral oximetry monitoring to guide treatment. Ann Thorac Surg. 2002;73:373-C.

4. Andropoulos DB, Stayer SA, Diaz LK, Ramamoorthy C. Neurological monitoring for congenital heart surgery. Anesth Analg. 2004. 99: 1365-75

5. Austin EH, Edmonds HL, Auden SM, Seremet V, Niznik G, Sehic A. Benefit of neurophysiological monitoring for pediatric cardiac surgery. J Thorac Surg. 1997. 114: 707-17

6. Bellomo R, Ronco C, Kellum JA, et al. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004; 8: 204-212.

7. Berens RJ, Stuth EA, Robertson FA, Jaquiss RD, Hoffman GM, Cava JR. NIRS monitoring during pediatric aortic coarctation repair. Pediatric Anesthesia. 2006. 16: 777-81

8. Booth EA, Dukatz C, Ausman J, Wider M. Cerebral and somatic venous oximetry in adults and infants. Surg Neurol Int 27-Nov-2010; 1:75

9. Bove, T., Covello, R. D., & Zangrillo, A. (2004). Acute renal failure and cardiac surgery.

10. Casati A, Fanelli G, Pietropaoli P, Proietti R, Tufano R, Montanini S. Monitoring cerebral oxygen saturation in elderly patients undergoing general abdominal surgery: A prospective cohort study. Eur J Anaesthesiol. 2006. 24: 59-65

11. Cerebral, N., Biomedical, M., Facility, I., & Interna-, H. (2013). A Comparative Study of Cerebral Microcirculation During Pulsatile and Nonpulsatile Selective Cerebral Perfusion : Assessment by Synchrotron Radiation Microangiography, 374–379. http://doi.org/10.1097/MAT.0b013e3182976939

12. Chertow, G. M., Levy, E. M., Hammermeister, K. E., Grover, F., & Daley, J. (1994). Independent Association between Acute Renal Failure and Mortality following Cardiac Surgery *, 9343(April 1987), 343–348.

13. Cho H, Nemoto EM, Yonas H, Balzer J, Sclabassi RJ. Cerebral monitoring by means of oximetry and somatosensory evoked potentials during carotid endarterectomy. J Neurosurg. 1998;89(4):533-538.

14. Denault A, Deschamps A, Murkin J. A proposed algorithm for the intraoperative use of cerebral NIRS. Semin Cardiothorac Vasc Anesth. 2007. 11: 274-81

15. Edmonds HL, Jr Ganzel BL, Austin EH 3rd. Cerebral oximetry for cardiac and vascular surgery. Semin Cardiothorac Vasc Anesth. 2004;8(2):147-166.

16. Edmonds HL Jr, Singer I, Sehic A, Strickland TJ. Multimodality neuromonitoring for neurocardiology. J Interv Cardiol. 1998;11(3):197-204.

17. Fenton KN, Freeman K, Glogowski K, Fogg S, Duncan KF. The significance of baseline cerebral oxygen saturation in children undergoing congenital heart surgery. Am J Surg. 2005. 190: 260-3

18. Ghanayem NS, Mitchell ME, Tweddell JS, Hoffman GM. Monitoring the brain before, during and after cardiac surgery to improve long-term neurodevelopmental outcomes. Cardiol Young. 2006. 16: 103-9

19. Gottlieb EA, Fraser CD, Andropoulos DB, Diaz LK. Bilateral monitoring of cerebral oxygen saturation results in recognition of aortic cannula malposition. Paediatr Anaesth. 2006. 16: 787-9

20. Heart Disease. (n.d.). Retrieved from http://www.cdc.gov/heartdisease/about.htm

21. Higami T, Kozawa S, Asada T, et al. Retrograde cerebral perfusion versus selective cerebral perfusion as evaluated by cerebral oxygen saturation during aortic arch reconstruction. Ann Thorac Surg. 1999;67(4):1091-1096.

22. Hoffman GM, Wider MD. Organ specificity of NIRS rSO2 measurements during regional ischemia in piglets. Anesthesiology. 2008. 109: A272

23. Iglesias I, Murkin JM, Bainbridge D, Adams S. Monitoring oxygen saturation significantly decreases postoperative length of stay: a prospective randomised blinded study. Heart Surg Forum. 2003;6:204.

24. Khilji, S. A., & Khan, A. H. (2004, July/August). Acute renal failure after cardiopulmonary bypass surgery. *Journal of Ayub Medical College, Abborrabad, JAMC, 16*(3), 8-25. Retrieved November 12, 2016, from Pubmed.

25. Kim MB, Ward DS, Cartwright CR, Kolano J, Chelebowski S, Henson LC. Estimation of jugular venous O2 saturation from cerebral oximetry or arterial O2 saturation during isocapnic hypoxia. J Clin Monit. 2000. 16: 191-9

26. Long, D. M., Jenkins, E., & Griffith, K. (2015). Perfusionist techniques of reducing acute kidney injury following cardiopulmonary bypass : an evidence-based review, 23–26. http://doi.org/10.1177/0267659114544395

27. Magruder, J. T., Crawford, T. C., Harness, L., Grimm, J. C., Suarez-pierre, A., Wierschke, C., … Barodka, V. (2017). ACQ A pilot goal-directed perfusion initiative is associated with less acute kidney injury after cardiac surgery. The Journal of Thoracic and Cardiovascular Surgery, 153(1), 118–125.e1. http://doi.org/10.1016/j.jtcvs.2016.09.016

28. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007; 11: 31.

29. Murkin JM, Adams SJ, Novick RJ, Quantz M, Bainbridge D, Iglesias I. Monitoring brain oxygen saturation during coronary artery bypass surgery: A randomized, Prospective Study. Anesth Analg. 2007. 104: 51-8

30. Poloschek CM, Sutter EE. The fine structure of multifocal ERG topographies. J Vis. 2002. 2: 577-87

31. Ranucci, M., Romitti, F., Isgrò, G., Cotza, M., Brozzi, S., Boncilli, A., … Donato, P. S. (2005). Oxygen Delivery During Cardiopulmonary Bypass and Acute Renal Failure After Coronary Operations. http://doi.org/10.1016/j.athoracsur.2005.05.069

32. Reflects Site-Specific Tissue Perfusion Noninvasively. (n.d.). Retrieved November 12, 2016, from http://www.medtronic.com/covidien/products/cerebral-somatic-oximetry/invos-5100c-cerebral-somatic-oximeter

33. Roberts KW, Crnkowic AP, Linnerman IJ. Near infrared spectroscopy detects critical cerebral hypoxia during carotid endarterectomy in awake patients. Anesthesiology. 1998;89(3A):A934.

34. Ruf, B., Bonelli, V., Balling, G., Hörer, J., Nagdyman, N., Braun, S. L., … Reiter, K. (2015). Intraoperative renal near-infrared spectroscopy indicates developing acute kidney injury in infants undergoing cardiac surgery with cardiopulmonary bypass : a case – control study, 1–11. http://doi.org/10.1186/s13054-015-0760-9

35. Sievert, A., & Sistino, J. (2012). A meta-analysis of renal benefits to pulsatile perfusion in cardiac surgery. The Journal of Extra-Corporeal Technology, 44(1), 10–14. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=22730858

36. Smith, M. N. A., Best, D., Sheppard, S. V. and Smith, D. C. (2008), The effect of mannitol on renal function after cardiopulmonary bypass in patients with established renal dysfunction*. Anaesthesia, 63: 701–704. doi:10.1111/j.1365-2044.2007.05408.x

37. Soltis, L. M., MSN, APRN, PCCN, CCRN-CSC, CCNS, FCCM. (n.d.). CCRN Review. Charlotte, NC: Med-Ed.

38. Tarzamni, M., Nezami, N., Rashid, R., Argani, H., Hajealioghli, P., & Ghorashi, S. (2008). Anatomical differences in the right and left renal arterial patterns. *Folia Morphol (Warsz)*, *67*(2), 104-110. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/18521808

39. Ward KR, Ivatury RR, Barbee RW, Terner J, Pittman R, Filho IP. NIRS for Evaluation of the Trauma Patient: A technology review. Resuscitation. 2006. 68: 27-44

40. Wider MD. Hemodynamic management and regional hemoglobin oxygen saturation of the brain, kidney and gut. J Perinatol Neonatol. 2009. 22: 57-60

41. Yao FSF, Tseng CC, Woo D, Huang SW, Levin SK. Maintaining cerebral oxygen saturation during cardiac surgery decreased neurological complications. Anesthesiology. 2001;95:A152.

42. Zarbock, A., Schmidt, C., Aken, H. Van, Wempe, C., Martens, S., Zahn, P. K., … Investigators, R. (2015). Effect of Remote Ischemic Preconditioning on Kidney Injury, 2133–2141. http://doi.org/10.1001/jama.2015.4189