

Review Article

Acute Kidney Injury Subsequent to Cardiac Surgery

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Abstract: Acute kidney injury (AKI) after cardiac surgery is a common and underappreciated syndrome that is associated with poor short- and long-term outcomes. AKI after cardiac surgery may be epiphenomenon, a signal for adverse outcomes by virtue of other affected organ systems, and a consequence of multiple factors. Subtle increases in serum creatinine (SCr) postoperatively, once considered inconsequential, have been shown to reflect a kidney injury that likely occurred in the operating room during cardiopulmonary bypass (CPB) and more often in susceptible individuals. The postoperative elevation in SCr is a delayed signal reflecting the intraoperative injury. Preoperative checklists and the conduct of CPB represent opportunities for prevention of AKI. Newer definitions of AKI provide us with

an opportunity to scrutinize perioperative processes of care and determine strategies to decrease the incidence of AKI subsequent to cardiac surgery. Recognizing and mitigating risk factors preoperatively and optimizing intraoperative practices may, in the aggregate, decrease the incidence of AKI. This review explores the pathophysiology of AKI and addresses the features of patients who are the most vulnerable to AKI. Preoperative strategies are discussed with particular attention to a readiness for surgery checklist. Intraoperative strategies include minimizing hemodilution and maximizing oxygen delivery with specific suggestions regarding fluid management and plasma preservation. **Keywords:** kidney injury, ischemia, cardiopulmonary bypass, perfusion. *JECT. 2015;47:16–28*

Acute kidney injury (AKI) is a common postoperative complication of cardiac surgery, and is associated with an increased risk of morbidity, mortality, and length of stay (1). The pathophysiology of AKI is complex and multifactorial, and the locus of injury is typically to the tubular cells and involves toxins (exogenous and endogenous), metabolic factors, ischemia–reperfusion injury, neurohormonal activation, inflammation, and oxidative stress. These various mechanisms are likely in play at different times, in different intensities, and some of them may act synergistically (2).

Risk factors for AKI include chronic kidney disease (CKD), albuminuria, hypertension, diabetes, advanced age, and obesity. Common contributors to AKI in the inpa-

tient setting are coronary artery bypass surgery and valve replacement surgery with cardiopulmonary bypass (CPB), gaseous and particulate emboli, contrast imaging agents, nephrotoxic drugs, sepsis, reduced renal blood flow, and hypotension. Some of the consequences are extended intensive care unit (ICU) stay, hospital stay, increased need for short- and long-term renal replacement therapy (RRT), progression of CKD, including end-stage renal disease (ESRD), and increased short- and long-term mortality.

AKI occurs in 2–30% of patients undergoing cardiac surgery, depending on the definition (3). Long-term survival in patients who undergo cardiac surgery is proportional to the severity of AKI, at least as assessed by peak changes in serum creatinine (SCr) (4). A dose–response relationship between severity of AKI and long-term survival has been demonstrated in several settings where the duration (in days) of creatinine elevation is associated with reduced 5-year survival (5). This effect on survival may not be directly related to the kidney injury. AKI may be a surrogate for other undetected organ injuries, an epiphenomenon that may be useful as a retrospective signal. The SCr elevation in the first postoperative 48 hours may indicate

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Table 1. Classification of AKI.

RIFLE Classification	
Risk	
Increase in sCr by 1.5 times from baseline or GFR decrease >25%	Urinary output <.5 mL/kg/h for 6 hours
Injury	
Increase in sCr by 2 times from baseline or GFR decrease >50%	Urinary output <.5 mL/kg/h for 12 hours
Failure	
Increase in sCr by 3 times from baseline or sCr \geq 4 mg/dL, or GFR decrease by 75%	Urinary output <.3 mL/kg/h or anuria for 12 hours
Loss	
Persistent need for renal replacement >4 weeks	
ESRD	
Need for RRT >3 months	
AKIN Classification	
Stage 1	
Increase in sCr by \geq .3 mg/dL or increase by 1.5–2 times from baseline	Urinary output <.5 mL/kg/h for 6 hours
Stage 2	
Increase in sCr >2–3 times from baseline	Urinary output <.5 mL/kg/h for >12 hours
Stage 3	
Increase in sCr by >3 times from baseline or absolute sCr \geq 4 mg/dL, with acute increase of \geq .5 mg/dL	Urine output <.3 mL/kg/h for 24 hours or anuria for 12 hours

AKIN, AKI Network; RIFLE, risk, injury, failure, loss, end-stage kidney disease.

Reprinted with permission from Robert AM, Kramer RS, Dacey LJ, et al. Cardiac surgery-associated acute kidney injury: A comparison of two consensus criteria. *Ann Thorac Surg.* 2010;90:194

that a renal injury has occurred. Considering the lag time between the injury and the SCr rise, it is likely that the injury occurs intraoperatively. Opportunities for preventative strategies lie in scrutinizing preoperative and intraoperative processes of care. The report from the Institute of Medicine in September 2012 underlined how failure to apply the best evidence at the point of care is a missed opportunity that can result in patient harm (6). Patient management plans substantiated by evidence is fundamental to decreasing unfavorable outcomes such as AKI.

The correlation of creatinine elevation with patient survival is significant, even when the creatinine returns to baseline before the patient is discharged from the hospital. As the renal injury may not be substantial enough to significantly impair toxin excretion and electrolyte balance, as an epiphenomenon, AKI may be a signal for adverse outcomes by virtue of other affected organ systems, a consequence of multiple factors. The kidney injury is in the context of a patient whose comorbidities and genetic predisposition define the preoperative status.

DEFINITION OF AKI

Earlier definitions of AKI were based on large, 1.5- to 2-fold increases in SCr (7). Lower creatinine thresholds have been developed to more rigorously define AKI, allowing us to better develop strategies to recognize and treat acute injury. Traditional definitions of AKI have been less sensitive to the magnitude of renal injury that may be detected by subtle elevations in SCr such as those used by the AKIN (Acute Kidney Injury Network) and RIFLE (risk, injury, failure, loss, ESRD) definitions (see Table 1). These two consensus criteria have been compared and the AKIN and

RIFLE criteria are both accurate and early predictors of mortality (8). More recently, the Kidney Disease: Improving Global Outcomes (KDIGO) Workgroup (9) has developed clinical practice guidelines for AKI based on AKIN and RIFLE classifications. Currently, creatinine levels are the most useful marker for detection of AKI.

The newer definitions with lower SCr levels defining AKI have provided more insight related to the onset, severity, and duration of AKI. In one such study, the duration of the rise in postoperative cardiac surgery SCr is associated with long-term mortality. Brown et al. (2) (see Figure 1) used the AKIN definition of AKI to analyze 4987 cardiac surgery patients in one center from 2002 through 2007 with SCr collection. AKI was defined as at least a .3 mg/dL or at least a 50% increase in SCr from baseline and further classified into AKIN stages. Duration of AKI was defined by the number of days AKI was present and categorized as

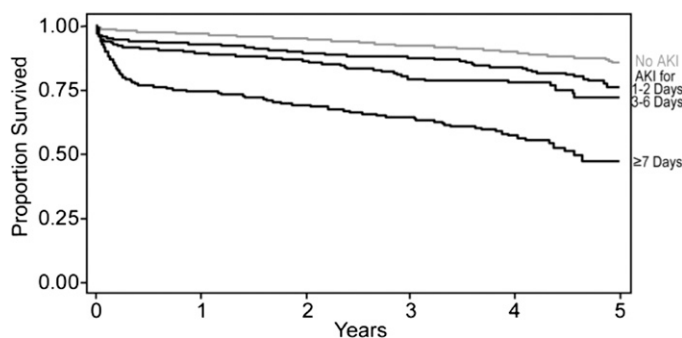


Figure 1. Survival by duration of AKI. The proportion of patients surviving from the time of cardiac surgery is plotted by the categories for the duration of AKI: no AKI (gray line), AKI for 1–2, 3–6, and \geq 7 days (black lines; $p < .0001$ by log-rank test) (2). Reprinted from *Ann Thorac Surg* 2010;90:1142–9 with permission from Elsevier.

Table 2. Pathophysiologic factors contributing to development of ARF (3).

Preoperative	Intraoperative	Postoperative
Lack of renal reserve	Decreased renal perfusion	Systemic inflammation
Renovascular disease	Hypotension	Reduced LV function
Prerenal azotemia	Lack of pulsatile flow	Vasoactive agents
Recent diuresis	Vasoactive agents	Hemodynamic instability
NPO status	Anesthetic effects	Nephrotoxins
Impaired LV function	Embolic events	Volume depletion
ACEI/ARB	CPB-induced inflammation	Sepsis
Nephrotoxins	Nephrotoxins	
Intravenous contrast	Free hemoglobin	
Other medications		
Endotoxemia		
Inflammation		

NPO, nothing by mouth.

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no AKI, AKI for 1–2 days, 3–6 days, and for at least 7 days. Long-term survival was significantly different by AKI duration ($p < .001$). Inasmuch as the duration of AKI after cardiac surgery is directly proportional to long-term mortality, the AKI dose-dependent effect on long-term mortality helps to close the gap between association and causation. Brown concluded that AKI stages and AKI duration have important implications for patient care and can aid clinicians in evaluating the risk of in-hospital and post-discharge death.

Tolpin et al. (10) found that subclinical changes in SCr were associated with increased 30-day mortality after coronary artery bypass grafting. In a retrospective analysis of 3914 cardiac surgery patients, they found that patients with smaller increases in SCr that did not meet AKIN or RIFLE definitions were associated with increased mortality. They went further to introduce the concept of a negative change in SCr (reduction in SCr), finding it associated with the lowest 30-day mortality. They hypothesized that tissue hypoperfusion, a more global insult, may be reflected in a rise of SCr, a consequence of muscle hypoxemia. That increase in SCr load on an injured kidney would result in the increase in SCr. On the other hand, well-perfused, well-hydrated patients may be more likely have lower SCr, a reflection of a combination of adequate oxygen delivery and hemodilution. Tolpin suggested “a slight change in serum creatinine (0–2 mg/dL) after cardiac surgery with CPB may mark a group of patients with early stages of organ dysfunction or tissue hypoperfusion” (10).

RISK MARKERS, PREVENTION, PATHOPHYSIOLOGY, AND SURVIVAL IMPLICATIONS

A number of preoperative and intraoperative practices may contribute to an increased incidence of AKI, especially in those patients identified as being the most vulnerable.

Prediction models for AKI have been described that are valuable tools to assist with the identification of at-risk patients (11,12). Preoperative checklists and the conduct of CPB represent opportunities for prevention. In their review of AKI, Rosner and Okusa (3) state that the kidneys are vulnerable to a myriad of hemodynamic, nephrotoxic, and inflammatory influences that may occur preoperatively (see Table 2). The most vulnerable patient to AKI is a patient who already has a measurable decrease in renal function, patients with poor renal reserve or renovascular disease. The preoperative patient may have had a recent diuresis, be fasting for procedures, or as is often the case in cardiac surgery, have impaired left ventricular function with poor cardiac output. When combined with other factors, the renal medulla, the part of the kidney most sensitive to poor oxygen delivery, suffers from a hypoxic injury if renal perfusion is compromised. Many preoperative patients are more predisposed to AKI as they are taking medications that affect the renin–angiotensin axis such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, or they have been exposed to nephrotoxins such as intravenous contrast or non-steroidal anti-inflammatory drugs, common over-the-counter analgesics.

Rosner and Okusa (3) go on to say that endotoxins may activate inflammatory mediators in the preoperative period that can set up the kidney for subsequent injury. Even in the absence of evidence for clinical infection, endotoxins have been detected in some patients that may be explained by sub-clinical catheter infections or poor cardiac output with intestinal ischemia with associated translocation of bacteria from the gastrointestinal tract. These patients could have a subtle renal injury that may not be reflected by changes in glomerular filtration rate (GFR) that could make a patient more vulnerable to AKI.

Patients with pre-existing renal disease are at the highest risk of suffering from AKI (3). The Northern New England Cardiovascular Disease Study Group developed a prediction rule to assist clinicians in identifying patients

with normal or near normal renal function who are at high risk of developing severe renal insufficiency (11). Their prediction model includes age, female gender, hypertension, congestive heart failure, white blood count over 12,000, peripheral vascular disease, intra-aortic balloon pump and re-operative coronary artery bypass grafting. Similarly, Mehren et al. (13) developed a model to predict contrast-induced nephropathy (CIN) after percutaneous intervention which may have a role in predicting AKI in preoperative cardiac surgical patients.

INFLAMMATION AND GENETICS

Clinical and genetic factors predispose patients to AKI. The genetic factors and many of the clinical factors cannot be modified while others can. The balance between the pro-inflammatory response and the compensatory anti-inflammatory response that modulates it is an area ripe for future therapeutic strategies. The maladaptive response pattern manifested by the systemic inflammatory response syndrome (SIRS) is a target for investigators such as those interested in the use of intraoperative corticosteroids (14). Meanwhile, the patient's own compensatory anti-inflammatory response to SIRS dictates how well the release of biologically active mediators prevail, as they are pro-inflammatory proteins that lead to organ dysfunction, including AKI.

Approximately 99.9% of the human genome is identical. The other .1% of the genome is composed of genetic polymorphisms that account for biologic diversity among individuals in a species. Studying genetic polymorphisms may be an opportunity to identify an individual's susceptibility to various phenomena such as SIRS related to CPB and their target organ response. The identification of these polymorphisms might be a future tool for identifying patients at the highest risk of poor tolerance to the inflammatory response to CPB (15).

DEVELOPMENT OF AKI: PREOPERATIVE EVENTS

Kidney injury likely occurs in the operating room and is characterized by a creatinine elevation signaling the event with a 48-hour lag time. Knowing modifiable factors that contribute to AKI may help to devise strategies to prevent AKI in the preoperative and intraoperative phases of care. Some of the modifiable factors have been described by Karkouti et al. (16) and include anemia, CPB duration, and perioperative red blood cell (RBC) transfusions.

According to Medalion et al. (17) iodinated contrast material causes a brief (minutes) period of vasodilatation that may be followed by sustained (hours to days) intrarenal

vasoconstriction and ischemic injury known as CIN. The ischemic renal injury sets off a cascade of events largely driven by oxidative injury, causing death of renal tubular cells. If a sufficient mass of nephron units is affected, then a recognizable rise in SCr will occur. That rise in creatinine may occur up to 48 hours after the injury. Performing a cardiac surgical operation during this vulnerable time frame may put the patient at risk for re-injury, an exacerbation of CIN.

An analysis by Marenzi et al. (18) revealed a correlation between the dose of contrast media and the incidence of CIN. Using a formula to determine the maximum acceptable contrast dose, Brown et al. (19) came to a similar conclusion, that is, the incidence of CIN increased with increasing contrast dose exposure. Both Brown and Marenzi found that patients commonly received contrast dye in excess of the maximum acceptable contrast dose and when the maximum acceptable contrast dose was exceeded, risk of CIN increased.

TIMING OF SURGERY

Patients having cardiac catheterization and cardiac surgery during the same admission were compared to patients having cardiac catheterization and cardiac surgery during separate admissions with regard to AKI (20). Patients often undergo surgery after cardiac catheterization during the same admission for reasons of instability and threatening anatomy as well as non-urgent reasons such as patient or provider convenience. When cardiac catheterization and cardiac surgery occur during the same hospitalization, there is an increased risk for AKI. Cardiac catheterization with discharge and readmission for non-urgent surgery may reduce the risk of AKI.

Ranucci et al. (21) assessed the efficacy of a policy limiting the practice of performing cardiac surgery in close succession to coronary angiography. They investigated the risk of AKI in patients undergoing angiography and cardiac surgery on the same day. In a study of over 4400 patients, they found that surgery on the same day of angiography significantly increases the risk of AKI. Limiting the practice of same day cardiac catheterization and cardiac surgery resulted in a decrease in the incidence of AKI. Such a simple policy change can aid clinical care teams in improving patient outcomes and quality of care. Hennessey et al. (22) found that preoperative cardiac catheterization within 24 hours of valve surgery increased the risk of acute renal failure (ARF) more than five-fold. In that analysis, postoperative ARF was defined as any patient with an increase of SCr to greater than 2.0 mg/dL and twice the most recent preoperative creatinine level or the requirement for dialysis postoperatively. They recommended that current practices be adjusted to ensure that

more than 24 hours have passed from the time of cardiac catheterization to valve surgery in elective settings.

DEVELOPMENT OF AKI: INTRAOPERATIVE EVENTS

The ultimate issue in the discussion of renal perfusion is oxygen delivery (DO_2) to renal tubular cells. Fifteen to thirty percent of the cardiac output goes to the kidneys, first going to the renal cortex and then to the renal medulla. Consequently, the blood arriving at the medulla, where the renal tubules mostly reside, is partially deoxygenated. Cells of the thick ascending limb of the loop of Henle in the medulla are extremely vulnerable to hypoxic damage. Margin for error is small and may be unforgiving when the components of the formula for DO_2 requirements are not satisfied, even for short periods of time. AKI is a conse-

quence of injured renal tubular cells located in the vulnerable renal medulla, underlining the importance of adequate oxygen delivery to renal medullary cells during CPB (3).

Ranucci et al. (23) investigated the role of the lowest oxygen delivery, lowest hematocrit, and pump flow during CPB as possible risk factors for ARF and renal dysfunction. They found that the best predictor for ARF and peak postoperative SCr levels was the lowest oxygen delivery, with a critical threshold at less than 272 mL/min/m^2 . Ranucci et al. concluded that excessive hemodilution during CPB is a risk factor for postoperative renal dysfunction and that increasing the oxygen delivery by increasing CPB flow rate may compensate for reduced oxygen carrying capacity related to hemodilution (see Figure 2).

The four elements of the formula for oxygen delivery in the setting of CPB are 1) pump flow, 2) hemoglobin, 3) oxygen saturation, and 4) arterial oxygen tension. Since the

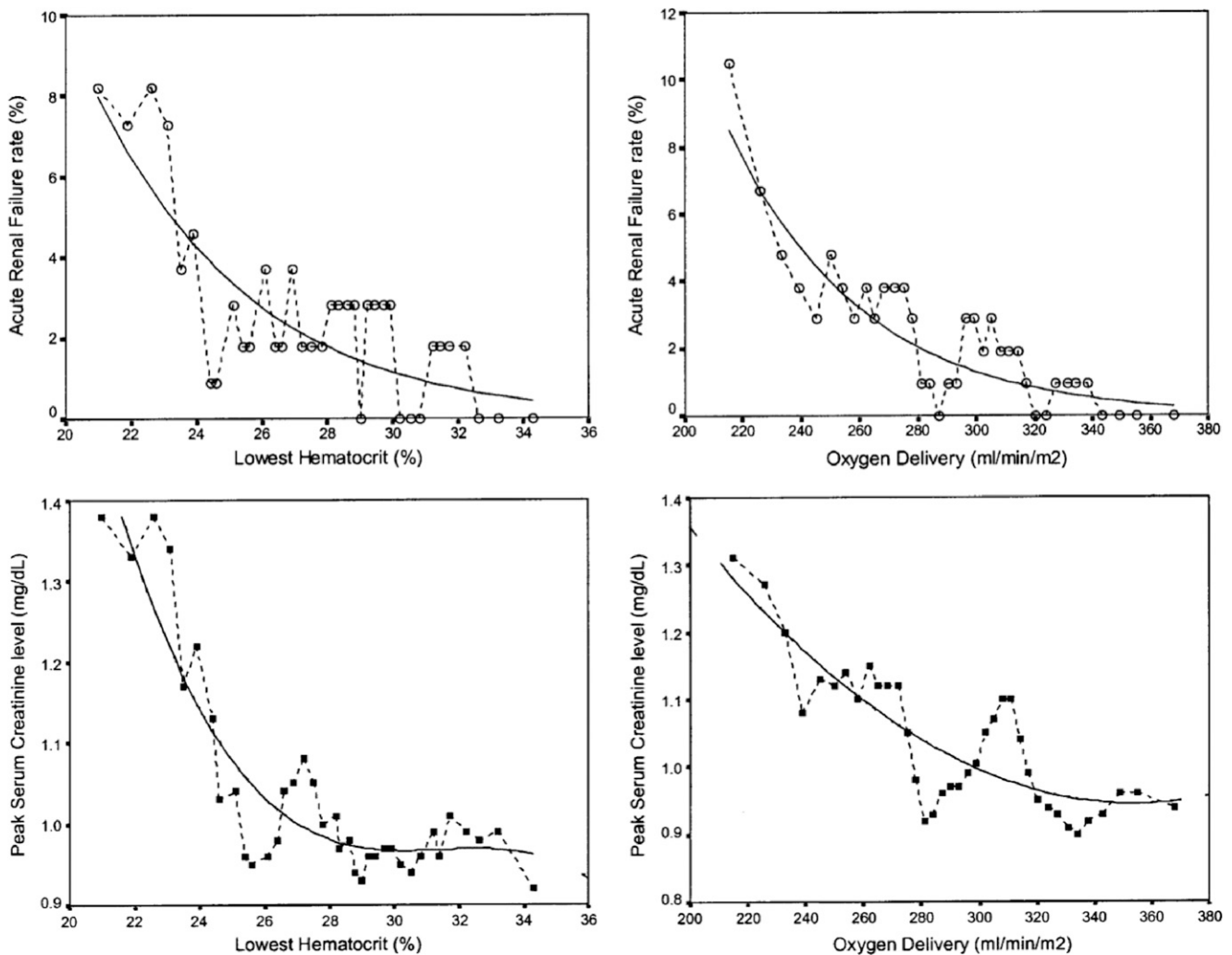


Figure 2. Oxygen delivery during cardiopulmonary bypass and ARF after coronary operations showing relationship (rolling deciles non-linear regression analysis) between the lowest hematocrit and lowest oxygen delivery during cardiopulmonary bypass and the ARF rate/peak postoperative serum SCr (23). Reprinted from *Ann Thorac Surg* 2005;80:2213–20 with permission from Elsevier.

formula for oxygen delivery is $DO_2 = \text{pump flow} (\text{Hb} \times 1.36 \times O_2 \text{ sat} + .003 \times pO_2)$, the four variables are easily measured and can be carefully monitored and adjusted appropriately, thereby improving the likelihood of adequate oxygen delivery to the renal medulla. de Somer et al. (24) addressed the issue of O_2 delivery and CO_2 production during CPB being determinants of AKI and whether it is time for goal directed therapy. They found that nadir DO_2 levels during CPB are independently associated with AKI. They postulated that since DO_2 during CPB is a modifiable factor through pump flow adjustments, that maintaining DO_2 level above the identified critical value might limit the incidence of postoperative AKI. In de Somer's analysis, Ranucci's earlier work (23) was confirmed as patients with nadir DO_2 levels below $262 \text{ mL}/\text{min}/\text{m}^2$ had a significant increase in AKI over those patients whose nadir DO_2 s were higher (see Figure 3).

The findings of de Somer and Ranucci make a strong case for monitoring DO_2 during CPB. There may be times when the decision of where to maintain the patient's perfusion flow rate and pressure may be based on experience rather than evidence and other times when low perfusion flow rates are tolerated at the request of the cardiac surgeon for technical reasons. Moment-to-moment adherence to maintaining oxygen delivery and satisfying all of the components of the DO_2 equation may help to avoid a

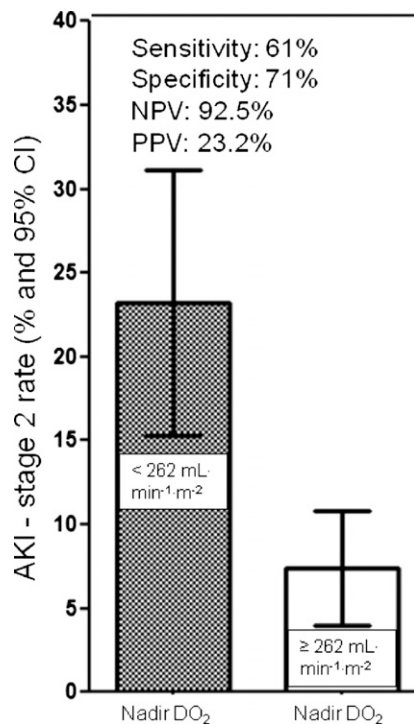


Figure 3. AKI rates in patient groups according to the critical values of DO_2 with sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) (24). Reprinted with permission from Critical Care Medicine 2011;15:R192.

nadir DO_2 below the critical level and decrease the likelihood of AKI. The discipline of maintaining adequate oxygen delivery requires cooperation and coordination among the members of the cardiac surgical team.

Of the three modifiable components of the DO_2 formula, finding the ideal level of hemodilution while maintaining an Hb high enough to deliver adequate O_2 to the tissues is the most challenging. Habib et al. (25) questioned whether current practice should be changed considering the danger of low hematocrits during CPB. They studied 5000 consecutive cardiac procedures and identified an association between nadir hematocrit during CPB and organ dysfunction and adverse clinical outcomes. The incidence of renal failure, multiorgan failure, and mortality as well as several other adverse events were significantly increased as the lowest hematocrit decreased below 22%. They concluded that the role of the perfusionist is to develop strategies to prevent low nadir hematocrits (<22%).

Maintaining hemodilution at safe levels is in the context of knowing that while low nadir hematocrits during CPB are associated with a higher mortality, transfusing those patients with allogeneic RBCs can make the outcome even worse. Surgenor et al. (26) showed that the management of hemodilutional anemia during surgery with RBC transfusion is associated with an increased risk of low output failure (LOF) irrespective of the extent of anemia. They defined LOF as: 1) placement of an intra-aortic balloon pump intraoperatively, 2) return to bypass for other than bleeding, or 3) the use of two inotropes 48 hours postoperatively. Perioperative transfusions were shown in to be one of the modifiable factors contributing to AKI in Karkouti's analysis (12). The goal is to keep the patient in the safety zone described by Loor et al. (27) (see Figure 4)

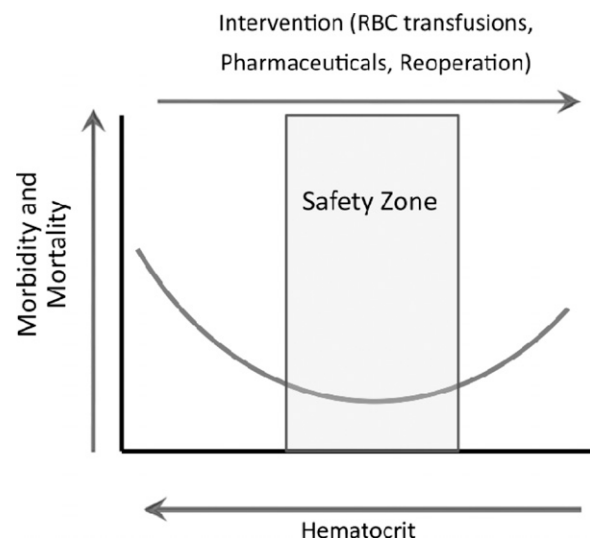


Figure 4. Management of anemia in cardiac surgery: finding the safety zone (27). Reprinted from J Thorac Cardiovasc Surg 2013;144: 538-46 with permission from Elsevier.

where finding the sweet spot in the relationship between low hematocrit and mortality was analyzed in the context of the risk of interventions such as transfusions, pharmaceuticals, and re-exploration. Although anemia is associated with worse results, transfusing those patients appears to be worse.

Excessive hemodilution can be avoided by minimizing the size of the CPB circuit as well as the amount of crystalloid added. Small circuits and retrograde autologous priming (RAP) decrease the amount of crystalloid added to the patient at the initiation of CPB. Small individuals, most of whom are women, tend to become the most hemodiluted, compounded by the higher incidence of anemia in females. Hemodilution can be minimized by small circuits, RAP, and minimizing crystalloid before CPB. By minimizing crystalloid, the perfusionist has the most control of the level of hemodilution, allowing the conduction of CPB to be in the ideal range, so that the rheology requirements of CPB and proper oxygen delivery are simultaneously satisfied (28–30).

DEVELOPMENT OF AKI: POSTOPERATIVE EVENTS

Given that the renal injury likely occurs in the operating room and that the elevation in serum creatinine is a delayed signal, the seven factors listed in Table 2 serve to further exacerbate the injury in a vulnerable kidney. AKI most often occurs in patients with acute insults on top of underlying comorbidities. Treatment for AKI includes correcting hemodynamic instability, especially in view of the fact that the injured kidney has lost its ability to autoregulate. That is, the kidneys, along with the heart and brain, have an intrinsic ability to autoregulate blood flow. In the case of the kidney, when the perfusion pressure falls, compensatory mechanisms that include vasodilatation allow blood flow to continue at the same rate as before. Losing that compensatory mechanism makes maintaining an adequate mean blood pressure one of the strategies in the management of AKI (31). Other treatment strategies include fluid and electrolyte management, RRT, avoidance of nephrotoxins, and time.

Management of a patient with AKI is focused on minimizing damage once the patient is post-operative. The next two sections address the preoperative and intraoperative opportunities to prevent AKI. Since AKI is likely a signal that the kidneys along with other end organs have sustained an injury, many of these opportunities have the potential to ameliorate effects on other target organs as well as the kidneys. The following section outlines specific preoperative and intraoperative strategies that can be considered for prevention of AKI associated with cardiac surgery.

CONSIDERATIONS FOR AKI PREVENTION: PREOPERATIVE

Avoidance of Preoperative Transfusions

Although there is evidence that perioperative RBC transfusions are associated with AKI (16), there is little evidence to support the practice of preoperative transfusions. In a single center pilot study, Karkouti et al. (32) hypothesized that prophylactic erythrocyte transfusion in anemic patients may protect against AKI. They did not show a difference in AKI between groups. They did note that there was a correlation between high transferrin levels in patients who received perioperative transfusions and AKI. In an accompanying editorial, Vincent and Lelubre (33) noted that Karkouti's results raised the question as to whether altered iron metabolism may contribute to organ dysfunction after major surgery.

Preoperative Statins

Tabata et al. (34) found that preoperative statins in cardiac surgery are renoprotective. They showed a renoprotective effect of preoperative statins but were unable to determine dose or duration or class of statin to use. A meta-analysis by Liakopoulos et al. (35) favored preoperative statins in cardiac surgery with significant differences being seen in all cause mortality, atrial fibrillation, and stroke. Five studies were included that addressed AKI without using the lower creatinine thresholds of AKIN or RIFLE, thereby did not show a significant difference. Statins improve endothelial function and decrease inflammatory markers.

Separation of Cardiac Catheterization and Cardiac Surgical Admission

It is ideal to avoid combining contrast exposure with surgery (20–22). If there are no compelling reasons for surgery such as instability or life-threatening anatomy, discharge and subsequent readmission may be indicated. If CIN occurs, surgery should be postponed if possible. Mehran et al. (13) have developed a prediction tool for CIN after percutaneous coronary intervention that may be useful with any contrast exposure. Prediction tools combined with risk stratification regarding patient's coronary anatomy and physiologic state may prove to be useful in determining delaying surgery to a subsequent admission.

Preoperative Glucose Management

Araujo de Azevedo et al. (36) observed that in critical illness, there was a significant correlation between the blood glucose levels and the incidence of AKI. Mehta (37) has stated that there is support for a direct contribution of hyperglycemia and insulin resistance to renal injury. The kidney has some compensatory responses to stress-related hyperglycemia with glycosuria. The consequences of insulin resistance, hypertriglyceridemia, oxidative

stress and decreased nitric oxide might directly drive the incidence of AKI. The kidneys are active in the process, and are also a target for new injury.

Establishing upper limits for high preoperative blood glucose levels and initiating basal-bolus insulin therapy or continuous insulin infusions when necessary is recommended in the Society of Thoracic Surgeons Practice Guideline Series: Blood Glucose Management During Adult Cardiac Surgery. In that review, Lazar et al. (38) stated that prior to cardiac surgery, it is reasonable to maintain blood glucose concentration ≤ 180 mg/dL.

Discontinuation of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers Preoperatively

Although somewhat controversial, there is a consensus that part of the challenge of postoperative vasoplegia may be related in part to the common use of medications that interfere with the renin-angiotensin axis (39). With some exceptions (39), it is generally accepted that discontinuing those medications at least 2 days before CPB may decrease the vasomotor paralysis often seen, decreasing the necessity for postoperative vasoconstrictors and excessive crystalloid administration (40–42).

Avoid Non-steroidal Anti-inflammatory Drugs and Aminoglycosides

Non-steroidal anti-inflammatory drugs (NSAIDs) are an example of a nephrotoxic medication that should be avoided preoperatively. Because of the large percentage of cardiac output received by the kidney, the renal arterioles and capillaries are especially vulnerable to pharmaceuticals (43). NSAIDs are commonly used over-the-counter medications and carry a risk of loss of renal function for two reasons. One mechanism is related to the decrease in prostaglandins, the mechanism that, although successful as an anti-inflammatory agent, reduces renal blood flow by disrupting the prostaglandin-mediated vasodilatory response to vasoconstrictor hormones that can result in deterioration of renal function. The second mechanism is acute interstitial nephritis, an immunological reaction that can occur in the renal interstitium after as little as 1 week of exposure to NSAIDs (44).

Aminoglycosides, in particular, single-dose prophylactic gentamycin in cardiac surgery, have previously been thought not to cause renal injury. Nielsen et al. (45) did a matched-pair analysis comparing patients that received single dose prophylactic gentamycin with patients who did not receive gentamycin. They found a significant difference in AKI using the AKIN definition in the two groups with greater fraction in the gentamycin group having AKI (22% vs. 17%; $p = .02$). In the context of cardiac surgery, where there are so many variables contributing to vulnerability to AKI, the superimposition of an aminoglycoside or NSAIDs could tilt the balance toward AKI.

Anemia Management

Diagnose and treat anemia if possible. Preoperative anemia is an independent risk factor for AKI (12). There is often not time to evaluate and manage anemic patients as many patients are urgent and require cardiac surgery during the cardiac catheterization admission. Many anemias are normocytic or microcytic, characterized as simple anemias or the anemia of chronic disease, a consequence of an inflammatory process that interferes with the absorption of iron and the inability to access iron stores. Simple anemias often respond well to intravenous iron, needing at least a week or more to show improvement in hemoglobin levels. Some patients with microcytic or normocytic anemia have had gastrointestinal or other blood loss. If a macrocytic anemia is not due to B12 or folic acid deficiency, it could be due to a hematologic malignancy.

Preoperative Infection

A white blood cell (WBC) count over 12,000 is one of the variables included in the prediction model used by the Northern New England Cardiovascular Diseases Study Group (NNECDSG) (11,46). In an NNECDSG analysis, they found that the preoperative WBC count across its entire observed range is a statistically significant predictor of in-hospital death and other adverse outcomes after coronary artery bypass grafting. Patients with a preoperative WBC count of at least 12,000 had an adjusted mortality rate 2.8 times higher than those with a WBC count less than 6000 (4.8% vs. 1.7%).

Vasoplegia Prophylaxis: Methylene Blue

Methylene blue in low doses (1.5–2.0 mg/kg) has been found to be safe and effective in managing the vasoplegic syndrome, especially when used prophylactically or as a first line drug. In the setting of CPB, high titers of pro-inflammatory mediators are released (e.g., cytokines, TNF- α , etc.) which stimulate the production of nitric oxide which promotes vasodilatation by the activation of the enzyme guanylate cyclase, which facilitates the production of cyclic guanosine monophosphate (GMP). Cyclic GMP causes vasodilatation. Methylene blue inhibits guanylate cyclase, essentially attenuating the severe vasodilatation/vasoplegia (47–49). The loss of vasomotor tone, common in postoperative cardiac surgical patients, precipitates a cycle of poor renal perfusion and the need to administer alpha agents or vasopressin and the potential to exacerbate AKI.

Readiness for Surgery Checklist

A comprehensive checklist agreed upon by team consensus with each item addressed in advance of each operation may influence modifiable preoperative factors that may contribute to a patient's vulnerability to AKI. This checklist may include such variables as discontinuation of medications that disrupt the renin-angiotensin axis,

administration of preoperative statins, anemia management, screening for hypercoagulability, managing preoperative infection, methylene blue for vasoplegia prophylaxis when indicated, separating admissions for cardiac catheterization and cardiac surgery when possible (especially if there is evidence for CIN), and preoperative glucose management. Using evidence-based checklists at every stage of the patient's experience assures the surgical team that, in the example of preoperative readiness, all has been done to assess and optimize the patient in preparation for the operating room. The ProvenCare® model from the Geisinger Clinic is an example of effective use of an evidence-based checklist (50).

CONSIDERATIONS FOR AKI PREVENTION: INTRAOPERATIVE

Decreased CPB and Cross Clamp Times

Long CPB and clamp times are associated with a higher incidence of cardiac surgery-associated acute kidney injury (CSA-AKI) (51–53). Increasingly complex cases can take more time and the acuity, co-morbidities, and anatomical challenges of these patients require more operating time, CPB time, and clamp time. Ideally, unavoidable fixed variables should be faced in the context of optimizing the patient preoperatively then increasing intraoperative workflow efficiencies whenever possible.

Minimizing Transfusions: Intraoperative Plasma Preservation

The 2011 Update to The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists Blood Conservation Clinical Practice Guidelines, states that “during CPB, intraoperative autotransfusion, either with blood directly from cardiomy suction or recycled using centrifugation to concentrate red cells, may be considered as part of a blood conservation program. Class of Recommendation IIb (Level of evidence C)” (54). While the cell saver saves RBCs, there is a loss of protein-rich plasma and platelets during its use that can be minimized by eliminating the use of cell saver while patient is heparinized, using instead the cell saver subsystem of the heart-lung machine, the cardiomy suction. Belway et al. (55) showed variability (a sign of non-evidence based practices) regarding use of the cell saver in Canada. Rubens et al. (56) pointed out that the evidence for neurocognitive impairment secondary to the use of the cardiomy suction is questionable. Rubens found that “contrary to expectations, processing of cardiomy blood before reinfusion results in greater blood product use with greater postoperative bleeding in patients undergoing cardiac surgery”.

In cardiac surgery requiring CPB, utilizing the cell saver in the non-heparinized patient is an opportunity to save

RBCs, and the use of the cardiomy suction in the heparinized patient is an opportunity to save both RBCs and plasma. Targeted use of the cell saver to preserve plasma helps preserve the endothelial glycocalyx, the dynamic layer of bound glycoproteins and fluids. Much of the glycocalyx is contributed by plasma, coating a healthy vascular endothelium. In their review of perioperative fluid management, Chappell et al. (57) make the point that, at any one time, the amount of plasma fixed within the endothelial surface layer is 700–1000 mL in humans. Plasma plays a vital role in preserving endothelial vascular integrity.

Minimizing Hemodilution and Transfusions: Modified Ultrafiltration

The 2011 Update to The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists Blood Conservation Clinical Practice Guidelines states that “most surgical teams re-infuse blood from the extracorporeal circuit (ECC) back into patients at the end of CPB as part of a blood conservation strategy. Currently, two blood salvaging techniques exist: 1) direct infusion of post-CPB circuit blood with no processing; and 2) processing of the circuit blood, either by centrifugation or by ultrafiltration, to remove either plasma components or water soluble components from blood before reinfusion. Centrifugation of residual CPB blood produces concentrated red cells mostly devoid of plasma proteins, whereas ultrafiltration produces protein-rich concentrated whole blood” (54).

Based on their review of the literature, the writers of the clinical practice guidelines concluded that the use of modified ultrafiltration (MUF) is indicated for blood conservation and reducing postoperative blood loss in adult and pediatric cardiac operations using CPB. (Class of Recommendation I, Level of Evidence A). They also concluded that centrifugation of pump-salvaged blood, instead of direct infusion, is reasonable for minimizing post-CPB allogeneic RBC transfusion. (Class of Recommendation IIa, Level of Evidence A).

Balancing Perioperative Transfusions, Nadir Hematocrit, and Oxygen Delivery

Karkouti showed that perioperative red blood transfusions are one of the independent variables associated with CSA-AKI (12). He found that “therapies aimed at mitigating preoperative anemia, perioperative RBC transfusions, and surgical re-exploration may offer protection against this complication.” Ranucci et al. (23) found that the best predictor for ARF and peak postoperative SCr levels was the lowest O₂ delivery with a critical value of 272 mL/min/m² and that hemodilution is an independent risk factor with the lowest predictive value cutoff being a hematocrit of 26%, unlike the Habib study that had a cutoff of 22% (25) (see Figure 2). Ranucci concluded that since a high degree of hemodilution during CPB is a risk

factor for postoperative renal dysfunction, increasing the O_2 delivery with an adequately increased pump flow might reduce the incidence of AKI. de Somer et al. found that nadir DO_2 level during CPB is independently associated with postoperative AKI, and DO_2 during CPB is a modifiable factor through pump flow adjustments. deSommer et al. (24) concluded that maintaining DO_2 level above the identified critical value might limit the incidence of postoperative AKI (see Figure 3).

Habib et al. (25) analyzed 5000 consecutive cardiac procedures for an association between nadir hematocrit (HCT) on CPB and organ dysfunction and outcome. The incidence of renal failure, multiorgan failure, and mortality, as well as several other adverse events were significantly increased as the lowest HCT decreased below 22%. Keeping that in mind, Surgenor et al. (26) came to the same conclusion with regard to the outcome of LOF (described as return to CBP, addition of an intra-aortic balloon pump intraoperatively or the need for two inotropes up to 48 hours postoperatively). Surgenor also found that although anemia was associated with a higher incidence of LOF, adding RBC transfusions was associated with worse outcomes (see Figure 5).

Finding the right balance between the harm of transfusions and the optimal tissue delivery is the dilemma described by Loor et al. (27) as they discuss the implications and management of anemia in cardiac surgery. Balancing the risk of allogeneic RBC transfusions, the hazard of a low nadir hematocrit and the need for adequate intraoperative tissue oxygen delivery requires a careful balancing act while the patient is on CPB. Frequent determination of DO_2 while on CPB may result in a greater percentage of perioperative transfusions administered on CPB when the patient may be more vulnerable to low DO_2 , rather than in the postoperative hours in the ICU.

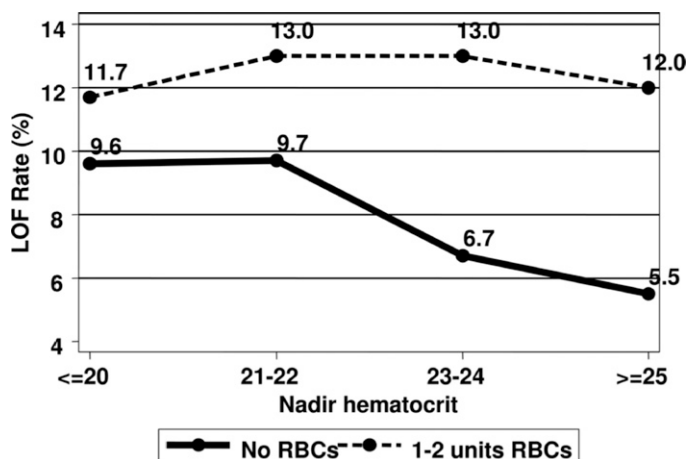


Figure 5. Crude risk of Low Output Failure (LOF) by Nadir Hematocrit during CPB. Reprinted with permission from Surgenor SD, et al. *Circulation* 2006;114(Suppl):43–8i.

Decrease Microemboli Associated with CPB

The conduct of CPB generates microemboli associated with brain injury and may be associated with kidney injury. Increased renal blood flow associated with hemodilution may increase the relative number of those emboli flowing to the kidneys, increasing the risk of AKI (58–60). The source of the microparticulate and macroparticulate emboli that may be responsible for renal injury in the multiple aortic clamping technique can be identified intraoperatively using epiaortic echocardiography to interrogate the ascending aorta. Most of the work published regarding epiaortic echocardiography has focused on the cerebrovascular implications (61–63). In an effort to delineate the population that would most benefit from epiaortic scanning during cardiac surgery, Schachner et al. described factors associated with the presence of ascending aortic atherosclerosis in cardiopulmonary bypass graft patients, concluding that epiaortic scanning should be carried out routinely for the detection of ascending aortic arteriosclerosis in patients with old age, hypertension, unstable angina, chronic obstructive pulmonary disease, cerebrovascular disease, peripheral vascular disease, elevated creatinine levels, high EuroSCOREs, and increased wall thickness of the descending aorta (64).

Minimize Hemodilution: Crystalloids

It is reasonable to minimize hemodilution by administering low crystalloid volumes before CPB and whenever possible. There are strategies that, by themselves, have a level of evidence and class of recommendation that is intermediate, that is, the benefit may exceed the risk. The classification used by the Society for Thoracic Surgeons Workforce on Evidence Based Surgery reported in the 2011 Update to The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists Blood Conservation Clinical Practice Guidelines classifies many interventions as 2b with an evidence level of B (54). These strategies may help to accomplish the goals of optimizing oxygen delivery and maintaining an optimal nadir hematocrit on bypass without the need for RBC transfusions.

Examples are the use of small circuits, retrograde autologous perfusion (RAP), and acute normovolemic hemodilution (ANH) (65). These interventions have been evaluated in limited populations such as single randomized trials or non-randomized studies and could be used as part of a multipronged approach to decreasing hemodilution, decreasing the administration of allogeneic RBC transfusions, and increasing the likelihood of delivering adequate oxygen to the tubules in the renal medulla.

RAP and ANH both have a Level of Evidence B and a Class 2b Recommendation. Although some practitioners are reluctant to introduce interventions with this level of evidence and recommendation, they are standards of care at many centers.

Blood Pressure Management and Cerebral Autoregulation Related to AKI

Kanji et al. (51) showed that a large difference (delta) in mean arterial pressure (MAP) and lower CPB flow during cardiac surgery are independently associated with early postoperative AKI in high-risk patients. In Kanji's study, delta MAP was defined as baseline MAP (acquired from three independent preoperative blood pressure readings) minus the average MAP on CPB (calculated as the average of MAP readings at 15-minute intervals during CPB). On the other hand, blood pressure management alone may not suffice in the prevention of AKI. Ono et al. found that blood pressure excursions below the cerebral autoregulation threshold during cardiac surgery are associated with AKI. By using near infrared spectrophotometry, Ono was able to determine the lower limit of cerebral autoregulation and found that it was independent of MAP. They concluded that monitoring the cerebral oximetry index could be a novel method to guide MAP targets during CPB (66).

Avoidance of Hyperthermic Perfusion During CPB

Newland et al. (67) found that hyperthermic perfusion during CPB and postoperative temperatures are independent predictors of AKI following cardiac surgery. In their analysis, they found an incidence of AKI of 12.3%, which was associated with a 4.5% increase in in-hospital mortality. Monitoring the arterial output temperature, they found that there was a 34% increase in AKI with each 10 minutes spent above 37°. They concluded that monitoring outlet temperature might help decrease the incidence of postoperative AKI following cardiac surgery using CPB.

Determine CPB Flow Based on Ideal Body Weight

Santambrogio et al. (68) describe using ideal body weight to determine CPB flow to avoid hemodilution. There is an increasing number of patients who are obese. CPB flow rate calculated on body surface area (BSA) is based on the assumption that each square meter of body mass, apart from the constitutional type of the patient, has the same metabolic rate. Since the major determinant of the metabolic rate is muscle rather than adipose tissue, and there is not a linear relationship between muscle and fat with regard to BMR, using the BSA in obese patients can result in CPB flows that are too high with an attendant increase in the potential for air emboli and the systemic inflammatory response (69,70). In a series of patients with body mass index (BMI) more than 30, they calculated the CPB flow rate and the heparin dose based on a BMI of 25. In their small study, they found that the transfusion rate was significantly lower in the treatment group, using a transfusion threshold of <8 g/dL of hemoglobin. Although this study is small, it represents another effort to avoid hemodilution and perioperative transfusions.

Albumin and AKI

The KDIGO Clinical Practice guidelines for AKI favor isotonic crystalloids over colloids in patients at risk for AKI (9). Frenette et al. (71) found that albumin administration is associated with AKI in cardiac surgery using a propensity score analysis. They found a two fold increased risk for AKI when they did the analysis both with and without postoperative hemodynamic instability. They used AKIN and RIFLE definitions. The use of albumin solutions as a volume expander is controversial and in the 2011 Cochrane Review of human albumin solution for resuscitation and volume expansion in critically ill patients the authors concluded that "in view of the absence of evidence of a mortality benefit from albumin and the increased cost of albumin compared to alternatives such as saline, it would seem reasonable that albumin should only be used within the context of well concealed and adequately powered randomized controlled trials (72)". Although the Frenette study was not designed to investigate underlying mechanisms to explain the effect on renal function, they did call attention to the fact that glomerular filtration pressure decreases as intracapillary oncotic pressure increases more than hydrostatic pressure, a situation favored by the use of hyperoncotic colloids (73).

Chloride and AKI

Yunos et al. (74) compared a chloride-liberal and a chloride-restrictive intravenous fluid administration strategy in critically ill adults and found a significant increase in AKI and the need for RRT in the chloride liberal group. It is hypothesized that there is a renal vasoconstrictive effect of tubular chloride reabsorption. Other possible mechanisms include tubuloglomerular feedback triggering glomerular afferent arteriole vasoconstriction and decreased glomerular filtration, thromboxane release from chloride infusion causing vasoconstriction and sensitivity to vasoconstrictive agents. Knowing that normal saline is not really normal, in the light of the effect of chloride on the kidney, it appears that balanced electrolyte solutions with low concentrations of chloride and avoidance of normal saline as well as colloid solutions with normal saline would be prudent (75).

SUMMARY

The long-term and short-term negative implications of AKI after cardiac surgery may not always be considered, especially when creatinine elevations are regarded as subtle and return to baseline before the patient is discharged. The opportunities to define new strategies for prevention of AKI primarily exist before and during the cardiac operation. Proper preparation of the patient for the procedure during which the renal injury is likely to occur and re-assessment of intraoperative practices represent

opportunities to incorporate multiple preventative strategies that have a multisystem focus.

In this review, we have described the pathophysiology of AKI following cardiac surgery and have detailed preoperative and intraoperative strategies that have the potential to prevent this complication. The preoperative strategies include a restrictive transfusion policy, statins, separating cardiac catheterization and surgical admissions, glucose management, discontinuing of medications interrupting the renin-angiotensin axis, avoidance of NSAIDs, anemia management, infection management, vasoplegia prophylaxis, and a readiness for surgery checklist. The intraoperative strategies include minimizing CPB and cross-clamp times, minimizing transfusions (intraoperative plasma preservation, MUF, minimizing hemodilution), optimizing oxygen delivery, decreasing microemboli, blood pressure management with attention to cerebral autoregulation, avoidance of hyperthermic perfusion, determination of CPB flow on ideal body weight, and minimization of albumin and chloride administration.

There are no conclusive studies to suggest that each of the strategies presented in this review alone or in combination will decrease the incidence of AKI after cardiac surgery. Each strategy represents a reasonable approach to care supported by evidence. AKI after cardiac surgery may be a signal that other systems are also injured leading to diminished short- and long-term patient survival. Careful analysis and mitigation of the factors that contribute to AKI may decrease short- and long-term mortality after cardiac surgery.

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