CHAPTER 42

Acute Kidney Injury in Cardiac Surgery

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OBJECTIVES

This chapter will:

1. Review the definition, epidemiology, and clinical consequences of cardiac surgery–associated acute kidney injury.
2. Discuss the mechanisms associated with acute kidney injury in patients undergoing cardiac surgery.
3. Review existing evidence and practice for prevention and treatment of cardiac surgery–associated acute kidney injury.
4. Consider the roles for novel biomarkers in risk stratification and management of cardiac surgery–associated acute kidney injury.

Acute kidney injury (AKI) is a common complication after cardiac surgery. The incidence of cardiac surgery–associated AKI (CSA-AKI) varies from 7% to 40%, depending on the patient population, the procedure, and how it is defined.[1–4] The incidence of CSA-AKI increases in patients with known comorbidities.[5,6] The severity of CSA-AKI fluctuates from subclinical AKI (an increase of biochemical markers of renal injury without a decrease in renal function) to severe AKI requiring renal replacement therapy. The development of AKI after cardiac surgery has a dramatic impact on intensive care unit (ICU) and hospital length of stay (LOS) as well as on short- and long-term mortality.[7–9] The presence of CSA-AKI may increase the odds of operative mortality three- to eightfold.[10,11]

The association between CSA-AKI and poor outcome has been recognized for many years. In the last couple of years, considerable progress has been made in understanding the pathophysiology of AKI and elucidating a more accurate definition of the syndrome. However, the prevention and management CSA-AKI remain a substantial challenge.

DEFINITION OF CARDIAC SURGERY–ASSOCIATED ACUTE KIDNEY INJURY

The RIFLE[12] and AKIN[13] criteria now have been well evaluated in studies investigating CSA-AKI.[5,14–16] However, it has been shown that the KDIGO criteria[17] have better prognostic power compared with the RIFLE or AKIN criteria.[18] This was confirmed in a single-center observational study in a general ICU population showing that the KDIGO criteria have greater sensitivity to detect AKI and predict in-hospital mortality.[19] Importantly, increases in serum creatinine may be attenuated in the setting of cardiac surgery because of perioperative transfusion and resuscitation.[20] Oliguria therefore may be more sensitive to AKI, particularly in the early stages of postoperative management. Several surgical scoring systems that incorporate serum creatinine levels and comorbidities have been developed to predict morbidity and mortality in cardiac surgery patients. The most commonly used are the Society of Thoracic Surgeons Score and the Euroscore II system to predict operative morbidity and mortality in adult patients after cardiac surgery.

PATHOPHYSIOLOGY OF CARDIAC SURGERY–ASSOCIATED ACUTE KIDNEY INJURY

AKI after cardiac surgery may be caused by many factors (Box 42.1), suggesting that CSA-AKI is the consequence of multiple interactive pathways. Several factors have been identified that are associated with an increased risk to develop CSA-AKI, including age, sex, preexisting cardiac dysfunction, preexisting chronic kidney disease (CKD), previous cardiac surgery, chronic obstructive pulmonary disease, and diabetes mellitus.[21] Perioperative administration of nephrotoxic agents, such as angiotensin-converting enzyme inhibitors, aminoglycoside antibiotics, loop diuretics, or radiocontrast dyes, may enhance the likelihood of developing a CSA-AKI.[21] These agents alone may not cause AKI, but the nephrotoxicity is related exponentially to the number of nephrotoxic insults, which includes hemodynamic instability or intravascular hypovolemia.

BOX 42.1

Cause of Cardiac Surgery–Associated Acute Kidney Injury

Cardiopulmonary Bypass
- Inflammation
- Hemolysis
- Hemodynamic instability

Shock
- Decreased renal perfusion
- Ischemic injury to remote tissues with release of damage-associated molecules (e.g., myoglobin)

Cardiac Dysfunction
- Low cardiac output
- Impaired right-heart function

Nephrotoxins
- Contrast
- ACE/ARBs
- NSAIDs
- Vancomycin

ACE, Angiotensin converting enzyme; *ARBs,* angiotensin receptor blockers; *NSAIDs,* nonsteroidal antiinflammatory drugs.

During cardiac surgery, several factors influence renal outcome. A multiplicity of damaging factors may cause kidney injury, including prolonged duration of cardiopulmonary bypass (CPB), systemic inflammatory response syndrome, prolonged aortic cross-clamping, severe bleeding requiring transfusion of blood products, requirement for potent vasopressors, prolonged hypotension, and low cardiac output syndrome that compromises perfusion pressure and renal blood flow.

CARDIOPULMONARY BYPASS

It was thought that the introduction of off-pump coronary artery bypass grafting (OPCAB) with the avoidance of CPB and its inflammatory response and hemolysis may reduce the incidence of CSA-AKI.[22] A meta-analysis of 22 randomized controlled trials (RCTs) with more than 4500 patients suggests that OPCAB may be associated with a lower incidence of CSA-AKI.[23] However, the conclusions of these studies were limited by different methodologic problems, including variability in the definition of AKI. In contrast, the German OPCAB in Elderly Patients trial, which recruited 1612 patients undergoing OPCAB versus coronary artery bypass grafting (CABG) with CPB, did not detect a difference in the incidence or severity of CSA-AKI.[5] Another large multicenter trial did not demonstrate a difference in the primary composite outcome measure of the 30-day rate of death, myocardial infarction, stroke, or renal failure requiring dialysis.[24] The same investigators performed a kidney function substudy of this main study by adding further renal data collection for patients after recruitment had already begun.[25] In this study, the risk of CSA-AKI was lower in the OPCAB group compared with the on-pump group (relative risk 0.75–0.89 depending on the definition of AKI used). However, although OPCAB was associated with a reduced rate of CSA-AKI, this was not associated with better outcomes at 1 year.[25] Importantly, chronic impairment in renal function was seen even in patients without clinical AKI after surgery, leading to concerns that some patients may experience subclinical AKI (injury undetectable without use of biomarkers) and be at risk for subsequent CKD—the relationship between AKI and CKD may be complex.[26]

Blood Pressure During Cardiopulmonary Bypass

The optimal mean arterial pressure (MAP) to prevent CSA-AKI during CPB is still unknown.[27] Most studies that investigate MAP during CPB have been observational and have tried to correlate hypotension with adverse neurologic outcome. Renal outcome studies have showed conflicting results.[28,29] Recently a single-center RCT was published, investigating 300 patients with known risk factors for AKI undergoing elective cardiac surgery with normothermic CBP.[30] In the control group, MAP during CPB was targeted to 50 to 60 mm Hg, whereas in the study group, the goal was a MAP of 75 to 85 mm Hg. The average MAP in the control and intervention groups was 60±6 and 79±6 mm Hg, respectively. There were no differences between the groups regarding the rate of CSA-AKI, hospital LOS, or mortality.

Contrast-Induced Nephropathy

Most cardiac surgery patients undergo contrast angiography or ventriculography before surgery. Many factors are known to be associated with the development of contrast-induced nephropathy (CIN), including type and dose of contrast medium, state of hydration, the patient's age, and degree of underlying CKD. A number of pathways are involved in development of CIN.[31] This may explain why no single intervention, including sodium bicarbonate, intravenous isotonic fluid hydration, N-acetylcysteine (NAC), and statins, among others, is able to prevent CIN.[32] Only intravenous isotonic fluid hydration remains recommended in guidelines that attempt to decrease the risk of CIN.[32]

An unresolved question is whether extending the time period between angiography and cardiac surgery can reduce the risk of CIN. It is recommended that in patients with preexisting renal dysfunction, a delay of surgery after coronary angiography may be reasonable until the effect of radiographic contrast material on renal function is assessed.[33] However, the evidence behind this recommendation is weak because it is based on retrospective, single-center epidemiologic studies using multivariable logistic regression demonstrating an increase in the odds ratio of CSA-AKI when surgery was performed less than 5 days after angiography.[34–36] However, another study demonstrated that time to surgery after angiography was not a risk factor for the development of CSA-AKI.[37] Based on the available evidence, the most reasonable approach is to evaluate for CIN before elective cardiac surgery but not to delay urgent surgery to allow a longer interval after angiography.

ASSESSING RENAL FUNCTION AND ACUTE KIDNEY INJURY

To predict or diagnose AKI, biomarkers and physiologic indicators have been studied. Although the RIFLE, AKIN, and KDIGO criteria have helped in defining and staging AKI, they all have important limitations. Serum creatinine and urine output have a low sensitivity and specificity, respectively.[38] Serum creatinine can be influenced by several factors (e.g., fluid therapy, muscle mass), and it does not accurately reflect kidney function (serum creatinine increases after more than 50% of the GFR is lost) and degree of tubular injury, whereas urine output can be influenced by diuretics and hypovolemia.[38] In addition, both markers cannot predict whether the kidney function improves or deteriorates.[39] Thus intervention of a therapeutic therapy based upon RIFLE, AKIN, or KDIGO criteria may be instituted far too late to alleviate perioperative AKI.[40] These limitations are thought to account for the poor clinical outcomes associated with AKI. Therefore the Acute Dialysis Quality Initiative (ADQI) has assigned the highest research priority to the discovery and/or standardization of new biomarkers of AKI.[41] In recent years, abundant papers on biomarkers have been published. Most of the studies investigated whether the different biomarkers can detect or predict AKI defined by serum creatinine-based definitions. Several promising biomarkers showed acceptable diagnostic performance for AKI up to 48 hours before a significant change in serum creatinine.[42] Because available point-of-care devices make it possible to measure biomarkers at the bedside within a short time frame (20 minutes), the community has shown great interest in integrating such biomarkers into clinical decision algorithms.

Neutrophil Gelatinase-Associated Lipocalin

Neutrophil gelatinase-associated lipocalin (NGAL) is a small protein linked to neutrophil gelatinase in specific leukocyte granules. It also is expressed in a variety of epithelial tissues associated with antimicrobial defense. In the normal kidney, only the distal tubules and collecting ducts stain for NGAL expression. Several studies have shown that NGAL is upregulated rapidly in the kidney very early after acute injury. The NGAL protein, which can be measured in the blood and in the urine, is one of the earliest and most robustly produced proteins in the kidney after nephrotoxic or ischemic AKI in animal models.[43] Urine and blood NGAL have been demonstrated to be an early predictor of AKI in several clinical scenarios, including trauma cardiac surgery.[44]

Haase-Fielitz et al.[45] performed a meta-analysis and looked for human biomarker studies that included NGAL in cardiac surgery, critical illness, and kidney transplantation. They identified 58 studies with more than 16,500 patients, including more than 7000 patients after cardiac surgery. Elevated NGAL levels predicted the development of AKI, with an impressive area under the receiver operator characteristic curve of 0.82 to 0.83. However, the authors also highlighted a number of limitations, including a lack of specific cutoff values for NGAL. Recently, a number of prospective studies have focused on NGAL in cardiac surgery. Omerika et al.[46] studied 150 patients undergoing cardiovascular surgery and concluded that urinary NGAL predicted postoperative AKI 24 to 48 hours earlier than elevations in serum creatinine levels that met RIFLE criteria. In a small study, Kidher et al.[47] demonstrated that plasma NGAL measured 3 hours after CPB was a much stronger predictor of AKI than serum creatinine levels.

Cystatin C

Cystatin C is a 13-kDa nonglycosylated cysteine protease inhibitor produced by all nucleated cells in a constant rate. In healthy subjects, plasma cystatin C is eliminated through glomerular filtration and completely metabolized by the proximal tubules. As cystatin C is not secreted in the tubular system, it normally is not found in urine. Therefore the presence of cystatin C in the urine reflects tubular damage.[48] A recent meta-analysis showed that plasma cystatin C is more sensitive in detecting smaller reductions and acute changes in glomerular filtration rate than serum creatinine.[49] However, plasma cystatin C levels can be influenced by

immunosuppressive therapy,[50] the presence of inflammation or malignancies,[51] and abnormal thyroid function.[52] Several studies demonstrated that changes in plasma and urine cystatin C can predict AKI.[53] Similar to serum creatinine, knowledge of the baseline is critical to interpretation of these filtration markers.

A number of studies suggest that cystatin C may be a useful early predictor of AKI in cardiac surgery patients.[6,54,55] In a prospective cohort study, investigators enrolled 1147 adults undergoing cardiac surgery and showed that preoperative cystatin C was superior to serum creatinine levels and eGFR in predicting the risk of postoperative AKI.[6] In contrast, another large study including 1150 high-risk adult cardiac surgery patients demonstrated that cystatin C levels were less sensitive than serum creatinine levels for detection of AKI but were able to identify which patients were at higher risk for AKI.[54] Wang et al.[55] found in a prospective study of 616 patients undergoing cardiac surgery that the level of preoperative serum cystatin C combined with the severity of proteinuria were accurate predictors of postoperative AKI.

TIMP-2 and IGFBP7

There are a number of other biomarkers that have been investigated in the last couple of years. Meersch et al.[56] studied urinary tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7), which are both inducers of cell-cycle arrest, in the mechanism of CSA-AKI. In 50 patients undergoing high-risk cardiac surgery with CPB, they found that increased urinary [TIMP-2] • [IGFBP7] levels 4 hours after CPB predict AKI.[56]

INTERVENTIONS TO PREVENT ACUTE KIDNEY INJURY

A number of studies have been performed in the past investigating different drug therapies and the timing of RRT to prevent AKI in patients undergoing cardiac surgery.

Statin Therapy

Some evidence suggests that stains may prevent AKI. However, most of the studies are on animals or are retrospective and inconclusive. Molnar et al.[57] investigated in 625 adult patients undergoing elective cardiac surgery operations the effects of continuing preoperative statins versus discontinuing them for 24 hours. There was no difference in AKI or need for renal replacement therapy (RRT). Interestingly, in patients who continued statins until the time of surgery, several renal biomarkers were significantly decreased, including urine kidney injury molecule-1 and urine and plasma NGAL. A recently published trial demonstrated that statins have no renoprotective effects in cardiac surgery patients.[58]

Early Initiation of Renal Replacement Therapy

The question of when to start RRT in patients with AKI is unresolved. Initiation of RRT means an escalation of therapy. Therefore one has to balance benefits against risks. The advantage of early initiation of RRT is to avoid complications such as hypervolemia, to eliminate toxins, and to correct acid-base homeostasis. However, on the other hand, patients can recover spontaneously from AKI without requiring RRT. A recently published systematic review and meta-analysis[59] analyzed nine retrospective cohort studies and two RCTs of early versus late initiation of CRRT in critically ill patients with CSA-AKI. This analysis included 841 patients. The overall results suggested that early CRRT was associated with shorter ICU LOS and decreased 28-day mortality. Similar meta-analyses also demonstrated a benefit from early initiation of CRRT.[60,61] However, the results have to be interpreted with caution because the studies used different definitions of "early" and "late" CRRT, and almost all studies are retrospective and observational. RCTs are required to definitely answer this important question.

Sodium Bicarbonate

Sodium bicarbonate may reduce tubular oxidative stress.[62] Therefore it has been investigated as a possible agent in preventing CIN. Because the results of available trials are contradictory, urinary alkalinization currently is not recommended for preventing CIN.[63] In addition, urinary alkalinization also has been proposed as a possible protective intervention in cardiac surgery. Turner et al.[64] recently published the results of a multicenter RCT of 0.9% isotonic saline versus sodium bicarbonate in patients at high risk for CSA-AKI. Because the interim analysis did not show a difference between the groups regarding the rate of CSA-AKI, the study was discontinued on the grounds of futility. Tian et al.[65] conducted a meta-analysis to investigate the effect of sodium bicarbonate in cardiac surgery. This study included five RCTs and one prospective observational cohort study. There was no difference in the occurrence of CSA-AKI.

Remote Ischemic Preconditioning

In addition to experimental evidence, extensive progress has been made in translating remote ischemic preconditioning (RIPC) from experimental models into clinical practice. Several clinical trials have been conducted thus far, and most suggest that RIPC may reduce kidney damage in humans (our review). However, some studies have found that RIPC has no effect on AKI. The reasons for the controversial results among different studies are manifold, including different patient populations, comorbidities, type of surgery, and RIPC protocols. The effects of RIPC on the kidney have been investigated extensively in the setting of cardiac surgery. In a large multicenter, randomized double-blind clinical trial, we recently found that RIPC in high-risk patients before cardiac surgery was effective for reducing the occurrence of AKI (37.5% vs. 52.5% with sham; ARR,15%; 95% CI, 2.56%–27.44%; $p = .02$). Furthermore, fewer patients receiving RIPC received RRT (5.8% vs. 15.8%; ARR, 10%; 95% CI, 2.25%–17.75%; $p = .01$).[66] Importantly, however, we found that the effectiveness of this intervention was associated strongly with the release of cell-cycle arrest biomarkers into the urine. A single-center, randomized trial (n = 120) also demonstrated that RIPC reduces the rate of AKI after cardiac surgery.[67] In line with these results, another small, randomized study demonstrated that RIPC reduced the postoperative peak creatinine serum concentration compared with the control intervention.[68] Furthermore, a retrospective study of nondiabetic patients undergoing elective CABG surgery showed that RIPC significantly reduced the incidence of

AKI.[69] In addition, two RCTs showed that RIPC also can reduce contrast-induced AKI in high-risk patient populations.[70,71] However, several studies have failed to demonstrate a beneficial effect of RIPC on kidney function.[72–78] One possible explanation for the negative results is that these studies involved low-risk patients and/or low-risk procedures and that for anesthesia they used propofol, a drug known to inhibit the effects of RIPC.[79,80]

Key Points

1. Cardiac surgery–associated acute kidney injury (CSA-AKI) is best defined by KDIGO criteria (creatinine and urine output criteria).
2. CSA-AKI occurs in approximately 7% of routine cases and in more than a third of patients with underlying risk factors or undergoing complex surgery.
3. Mortality and costs are significantly affected by CSA-AKI.
4. Numerous mechanisms are associated with AKI in patients undergoing cardiac surgery, including nephrotoxic (free hemoglobin, drugs, contrast) and hemodynamic (cardiorenal, shock).
5. There are no universally accepted methods to prevent or treat CSA-AKI. Early RRT appears to be advantageous when compared with late RRT, but patient selection for RRT is still a subject of debate.
6. Several novel biomarkers appear to add in risk stratification for CSA-AKI and may improve delivery of care to patients at highest risk.

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A complete reference list can be found online at ExpertConsult.com.

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