Emerging Concepts in Acute Kidney Injury Following Cardiac Surgery

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Abstract

Acute kidney injury (AKI) remains a significant cause of morbidity and mortality following cardiac surgery. Through a more thorough understanding of perioperative genomics and the evolving role of early biomarkers of AKI, the authors seek to improve meaningful outcomes among cardiac surgery patients. In this review, the focus will be on advances in risk stratification, evolving definitions and improving early diagnosis of AKI, identification of effective individualized therapies, and future directions.

Keywords

acute kidney injury; cardiac surgery; genetic polymorphism; biomarker; risk stratification

Improving Risk Stratification

Existing Risk Models

A reliable risk prediction model is essential to reduce the risk of mortality associated with postoperative AKI. Such a model permits risk reduction through individualized
perioperative management plans (Figure 1). Although no consensus exists regarding the optimal method of risk stratification, many attempts have been made to accurately predict which patients are at greatest risk.\textsuperscript{1,3,9-11} Chertow et al\textsuperscript{3} developed one of the first models to predict postoperative AKI requiring dialysis among a large prospective cohort of veterans undergoing cardiac surgery. Many other groups have subsequently developed their own single-center derived scoring systems, including the Cleveland Clinic Foundation, Toronto, and more recently Brazil, with the Acute Kidney Injury following Cardiac Surgery score.\textsuperscript{9-11} Most of these models use similar types of variables, including preexisting comorbidities, nature of the surgery, and physiologic insults. Specific risk factors identified across all models include advanced age, diabetes, congestive heart failure, low cardiac index, preexisting renal dysfunction, and more complex cardiac surgery. The Acute Kidney Injury following Cardiac Surgery score sought to improve predictive accuracy by incorporating intraoperative and postoperative factors as well as the preoperative risks considered by the other models. All of these models demonstrated good discrimination between their study groups and validation data sets.

Despite clear associations between known risk factors and AKI, these models consistently underestimate the risk of AKI, especially in populations at higher risk.\textsuperscript{12,13} Uchino et al\textsuperscript{12} studied 6 predictive scoring systems (4 AKI-specific systems and 2 general intensive care unit scoring systems) in a multinational registry of patients who either received or met criteria for renal replacement therapy. All scores had an area under the receiver operating characteristic curve of less than 0.7, suggesting that discrimination and calibration to predict AKI was poor when applied to a broad population. Candela-Toha et al\textsuperscript{13} compared the Toronto and Cleveland clinical scoring systems for AKI post–cardiac surgery. Although they demonstrated good discrimination comparatively with AUROC curve of 0.86 and 0.82, respectively, calibration was poor and there was underestimation of the risk of AKI except with patients within the very low risk category. Recalibration improved the predictive performance of both models, suggesting that variability in patient populations likely accounts for some of the underestimation of risk. Nonetheless, known demographic risk factors have been noted to account for only a small portion of the variation in postoperative creatinine levels.\textsuperscript{14} Thus, existing predictive models have moderate performance but remain insufficient with many factors that are unaccounted and persist despite careful consideration of known patient and surgical factors.

**Genetic Susceptibility**

Over time, predictive models are likely to improve as our understanding of the most relevant clinically observable risk factors increases. However, some of these risk factors may be elucidated by the emerging field of perioperative genomics. Traditional methods of identifying genetic associations rely on multigenerational studies; however, these studies are highly impractical to conduct in the field of perioperative medicine. Using association studies, numerous genetic polymorphisms have been identified that predispose patients to AKI in the face of similar surgical and physiologic insults. In brief, the majority of these high-risk genetic variants are associated with elevated risk of AKI through gene products that may contribute to a proinflammatory state, modulate the response to oxidative stress, or alter renal vascular responsiveness via augmentation of vascular tone. Although several polymorphisms have been investigated, most studies have focused on a select number of individual genes in small homogenous sample populations. Overall, the results have been variable and often inconsistent across studies (J. C. T. Lu, S. G. Coca, U. D. Patel, L. Cantley, and C. R. Parikh, A Search for Genes That Matter in Acute Kidney Injury: A Systematic Review. Journal of American Society of Nephrology. 2008:19(Supp.), 1177A.). The lack of robust and reproducible associations is not surprising, given the complex and multifactorial nature of perioperative renal injury. In addition, we have a rudimentary
understanding of how individual genes may contribute to phenotypes that may be at increased risk for AKI. Furthermore, none of these studies combined the prognostic information from genetic polymorphisms with existing predictive models. Nonetheless, some newer studies have provided greater evidence linking several genetic variations to AKI using larger populations.

**Proinflammatory genes**—Cardiac surgery results in a significant systemic inflammatory response associated with cardiopulmonary bypass (CPB), ischemia–reperfusion injury, and endotoxemia from splanchnic hypoperfusion. As a result, inflammatory mediators are elevated in postoperative cardiac surgery patients and have been associated with greater risk of renal injury. Thus, patients who are genetically predisposed to an exaggerated immune response may also be more susceptible to postoperative AKI. In fact, the interleukin-6 (IL-6) -174C and -572C alleles have been associated with increased IL-6 levels after cardiac surgery and with increased risk of AKI in this population. Similarly, the tumor necrosis factor-α -308A allele has been found to be weakly associated with increased risk of AKI, but this finding has not been reproducible across multiple studies. Finally, patients with multiple proinflammatory genetic polymorphisms appear to have an additive risk of AKI.

**Renal vascular tone modulators**—Polymorphisms of modulators of renal vascular tone have also been proposed as mediators of increased renal risk, including angiotensin-converting enzyme insertion/deletion, angiotensinogen, angiotensin receptor 1, and endothelial NO synthase. However, with the exception of a single positive study, no significant associations have been found.

**Miscellaneous individual polymorphisms**—Apolipoprotein E (APOE) is important to lipoprotein metabolism and immunomodulation. As a result, it has been linked to coronary disease, aortic atherosclerosis, and Alzheimer's disease. It possesses 3 alleles: APOE ε2, ε3, and ε4. Although the ε4 polymorphism has been associated with a smaller postoperative rise in creatinine, this finding has not been consistent across multiple studies. As oxidative stress due to reactive oxygen species has been implicated in the pathophysiology of renal injury, genetic variations that affect prooxidant and antioxidant gene expression have been studied as contributors to postoperative risk. A C to T substitution at the +242 position of NADPH oxidase p22phox has been associated with a 2.1-fold risk for the outcome of dialysis or hospital death. The haptoglobin 2-2 polymorphism was associated with increased AKI risk in a single-center trial after adjustment for confounding factors. Thus, our current understanding of the effect of the individual's genetic polymorphisms on overall risk of renal injury is that it appears modest at best.

**Linkage disequilibrium and the importance of multigene testing**—As with clinical predictors of risk, genetic factors are both myriad and frequently interrelated, making the development of a genomic risk profile difficult without first obtaining a more thorough understanding of human genotypes and haplo-types. When evaluating genetic predisposition, an important genomic phenomenon to consider is linkage disequilibrium—the nonrandom association of alleles at 2 or more loci. These alleles may be difficult to identify without genotype-wide studies, as they may not reside on the same chromosome. This has significant implications: Important polymorphisms may be overlooked if they are only clinically significant in the presence of other associated polymorphisms, or a single polymorphism may be falsely interpreted as significant because of its increased frequency in association with other high-risk genes. As a result of these limitations to association studies,
the next step in refining our understanding of at-risk genotypes will require large prospective studies of patients who develop AKI. The ideal model for such clinical studies will continue to be cardiac surgery for several reasons: this represents a high-volume surgical population, the epidemiology of AKI in this setting is well characterized, the timing of the injury is measurable, and improved risk prediction may translate into definable management strategies in the future.

Evolving Definitions and Detection

Defining Acute Kidney Injury

Although advancements in studying AKI continue, one of the most important barriers to high-quality studies is the lack of uniform definition.\(^1\),\(^29\)-\(^32\) This inconsistency makes it very challenging to compare and contrast results between studies. The Society of Thoracic Surgeons describes 2 separate clinical entities: postoperative renal insufficiency is defined as a 2-fold or greater elevation of creatinine that must exceed 2.0 mg/dL, whereas renal failure is defined as AKI requiring dialysis.\(^30\) In contrast, definitions that are associated with a grading system for AKI have been proposed by the Acute Kidney Injury Network (AKIN) group.\(^32\) Similarly, another graded classification system, named the RIFLE (Risk, Injury, Failure, Loss, and End stage) criteria, has been put forth by the Acute Dialysis Quality Initiative. In an attempt to standardize the definition of AKI across the scientific community, this system grades AKI based on urine output or change in creatinine from baseline.\(^31\),\(^32\) Recent studies have sought to determine the relative advantages between these criteria; however, there is no clear consensus.\(^33\),\(^34\)

Although the AKIN and RIFLE criteria provide useful graded definitions for AKI in clinical studies, multiple definitions remain in widespread use that define AKI only in terms of changes in creatinine, urine output, or the need for dialysis. For a variety of reasons, these arbitrary definitions of AKI are limited. Although serum creatinine performs reasonably well for estimating kidney function among patients with stable chronic kidney disease, it provides a poor measure of kidney function, particularly in the acute stages of renal dysfunction. It is well known that creatinine is influenced by numerous factors independent of the kidney, including gender, age, race, muscle mass, diurnal variation, metabolism, volume of distribution, medications, and protein intake.\(^35\) In addition, because of extensive intrinsic renal reserve, the glomerular filtration rate must decrease by approximately 50% before serum creatinine changes significantly from baseline.\(^5\),\(^6\) Furthermore, rises in serum creatinine often lag behind the initial renal injury by 48 to 72 hours (Figure 2).\(^36\) Urine output is similarly unreliable because it is influenced by a multitude of factors and may remain elevated in the presence of significant AKI.\(^35\) Finally, renal injury that is sufficiently severe to require dialysis is a relatively rare outcome following cardiac surgery. Although dialysis requirement provides a hard outcome to evaluate in clinical studies, using this definition alone without including milder grades of renal injury limits our ability to expand our understanding of perioperative AKI.

Despite the relative advantages of using standardized and graded definitions for AKI, they remain limited because they are still based on changes in either serum creatinine or urine output. In addition, serum creatinine may change in the absence of true renal tubular injury. However, a variety of novel bio-markers are elevated only in the presence of tubular injury or before rises in serum creatinine. Thus, these biomarkers have the promise of improving both the sensitivity and specificity of detecting ischemic AKI. With this promise, however, their arrival also adds to the conundrum of how AKI can be defined.

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Improved Detection With Biomarkers

Given the limitations of using serum creatinine and urine output for detecting AKI, there is a need for better biomarkers that can more reliably help diagnose AKI that is specifically caused by acute tubular necrosis, the most common renal injury among post–cardiac surgery patients. If such a diagnosis could be accurately detected early after the injury, then the “window of opportunity” for effective therapies may shift dramatically. In addition, earlier and more reliable detection of AKI would facilitate better risk stratification (Figure 3). Examples of outcomes that could be estimated include the degree of AKI including dialysis requirement, duration of AKI, subsequent chronic kidney disease, or mortality.

Prompted by these potential benefits of an improved biomarker for detecting AKI, several new biomarkers have been identified while those previously known have been more intensely studied. Although there have been more than 20 unique biomarkers of AKI identified or under investigation, most of the current interest has focused on a handful of promising biomarkers: neutrophil gelatinase–associated lipocalin, cystatin C, interleukin-18, and kidney injury molecule-1.37

Neutrophil gelatinase–associated lipocalin (NGAL)—NGAL is an immunological protein that is covalently bound to gelatinase from neutrophils and expressed at low levels by various human tissues, including the kidneys. In the setting of cardiac surgery, NGAL has been demonstrated to be a highly sensitive and specific biomarker of postoperative AKI.38-40 Its gene is one of the earliest and the most upregulated in the kidney after ischemic injury.38 In a study of 71 children undergoing CPB, the incidence of AKI was 28%.38 Both urine and serum NGAL increased 2 hours after CPB and were found to be the most powerful independent predictors of AKI in this population. Two additional studies have demonstrated that both urine NGAL (at 2 hours) and plasma NGAL (at 12 hours) strongly correlate with mortality in children.39,41 Similar results have been observed in the adult cardiac surgical population.40 In a study of 81 adult cardiac patients, 20% of the patients developed postoperative AKI. NGAL was higher in patients with AKI at 1 hour, 3 hours, and 18 hours post-CPB when compared with their non-AKI counterparts. A more recent study found that the use of aprotinin versus epsilon amino-caproic acid in patients undergoing cardiac surgery resulted in a 2-fold incidence of AKI in the aprotinin group. Urinary NGAL was significantly higher at both 0 and 3 hours post-CPB in patients receiving aprotinin.42

Interleukin-18 (IL-18)—IL-18, a proinflammatory cytokine that belongs to the IL-1 superfamily, has been shown to be both a mediator and biomarker of ischemic AKI. In a study of 55 children following CPB, urine IL-18 was detectable at 4 to 6 hours, peaked at 12 hours, and remained elevated for more than 48 hours.43 Further multivariate analyses suggested that urine IL-18 may also be a marker of AKI severity. Similar results have also been observed in noncardiac populations with AKI.44-46

Kidney injury molecule-1 (KIM-1)—KIM-1 is an immunoglobulin superfamily transmembrane protein normally present at low levels in proximal renal tubular cells that dramatically increases in expression following acute ischemic or nephrotoxic insult.47 Recent findings in cell cultures also demonstrate that it transforms renal epithelial cells into semiprofessional phagocytes that may assist with clearance of apoptotic and necrotic cells that result from AKI.48 Several studies among noncardiac patients have demonstrated that KIM-1 is a very sensitive indicator of AKI.47,49,50 However, fewer studies exist in the cardiac surgery literature specifically. In a cohort study of 103 adult patients undergoing CPB, KIM-1 levels increased significantly at both 2 hours and 24 hours postoperatively in patients with AKI.51 Similar results were found in a small case–control study of 40 pediatric patients following CPB.52
Cystatin C—Cystatin C is a protein that is produced by all nucleated cells.\textsuperscript{53} It has been suggested that cystatin C is an ideal molecule for measuring glomerular filtration rate because it is freely filtrated by the glomerulus, completely reabsorbed by the proximal convoluted tubules, and is not secreted.\textsuperscript{53,54} Unlike creatinine, it is not affected by age, gender, sex, or body mass.\textsuperscript{54} There have only been a few studies to date that have explored cystatin C as a biomarker for AKI post–cardiac surgery.\textsuperscript{55,56} In one prospective study, both serum cystatin C and NGAL were measured in 129 pediatric patients following CPB for corrective congenital heart surgery.\textsuperscript{55} Both cystatin C and NGAL were very strong independent predictors of AKI when compared with creatinine. In the 41 patients who developed AKI, NGAL levels were elevated 2 hours postoperatively, whereas cystatin C levels were elevated at 12 hours postoperatively. In another prospective study, cystatin C and NGAL were measured in both serum and urine samples of 72 adults who underwent cardiac surgery.\textsuperscript{56} Within the first 6 hours, serum values for both cystatin C and NGAL were not predictive of AKI whereas urinary values were elevated. These findings suggest that urinary biomarkers may be superior to serum values for early detection of AKI.

Diagnostic Issues With Biomarkers

Despite the promise for earlier AKI detection with greater sensitivity, every biomarker has its limitations. NGAL may be influenced by preexisting renal disease as well as infections.\textsuperscript{57,58} KIM-1 is specific to ischemic and nephrotoxic causes of AKI and may not be useful in detecting other types of renal injury.\textsuperscript{47,52} IL-18 peaks later than many other leading biomarkers at 4 to 6 hours postoperatively and is also more specific for ischemic insults of AKI.\textsuperscript{43} Finally, cystatin C is not specific for ischemic AKI and increases in its serum value occurs much later than NGAL, KIM-1, and IL-18.\textsuperscript{55}

In addition to their individual limitations, a variety of statistical and methodological issues must be appropriately considered when determining the overall diagnostic performance of biomarkers. First, odds ratios or relative risks alone are inadequate to discriminate between individuals who may or may not have AKI. Rather, the accuracy and validity of biomarkers are better summarized using AUROC curves.\textsuperscript{59} Next, errors in the reference standard may threaten the validity of biomarker studies but may be addressed by using hard outcomes (eg, dialysis-requiring AKI, death) that are not subject to the same potential for misclassification that is inherent in diagnosing AKI. Additionally, risk prediction in individual patients requires that the biomarker has strong discriminatory characteristics that include a large difference in risk between low and high values of the biomarker. Finally, the diagnostic characteristics of biomarkers will need to be evaluated with a consistent gold standard at well-defined time points. Although determining their individual test characteristics will represent a significant advance in this field, combinations of biomarkers in multimarker panels may provide a leap forward with the ability to differentiate between various AKI phenotypes and detect ischemic AKI earlier with greater precision and prognostic capacity.

Identifying Effective Therapies

Limitations of Previous Studies

AKI does not represent a single clinical entity; rather, it is a constellation of many disease processes and pathophysiologies. Although ischemic acute tubular necrosis is the most common form of renal injury following cardiac surgery, a number of renal insults of varying phenotypes may develop.\textsuperscript{60} For example, AKI in some patients who undergo cardiac surgery may be related to administration of aprotinin instead of ischemic tubular necrosis.\textsuperscript{61} In addition, the adult cardiac surgery population is very heterogeneous, and patients commonly have numerous comorbidities that vary between study populations.\textsuperscript{62} Among heterogeneous populations with multifactorial etiologies of renal insult, it is not surprising that specific
renal interventions have not consistently shown benefit. Many of the positive trials reported in the literature arise from the pediatric CPB population, which is more homogeneous and, therefore, more predictable.\textsuperscript{39,41,43,52,55}

Perhaps the most important barrier to studying therapeutic agents for the treatment of AKI is the lack of consensus regarding what constitutes a meaningful outcome. Is it a sustained reduction of creatinine by 50%, avoidance of dialysis dependency, protection from death, or even a decrease in a measurable biomarker? The inconsistencies in the current literature with respect to the definition of AKI and renal recovery need to be resolved so that future research can be meaningful, reproducible, and comparable.

Another major obstacle to finding successful treatments for AKI has been the conduct of trials adequately powered to show a benefit. Mortality, although extremely high in patients with severe AKI, is still relatively rare in postoperative cardiac surgical patients.\textsuperscript{1,2,5} To power a study for an absolute reduction in mortality, the necessary sample size would be immense. Such a study would require a large multicenter design and would be very costly.

Alternatively, clinical endpoints for therapeutic trials could include surrogate outcomes to identify the most promising agents for larger studies. Such surrogate outcomes could include changes in biomarker levels. However, biomarkers must first demonstrate strong, independent, graded, and consistent associations with relevant clinical outcomes. Potential designs could include randomization to biomarker measurement followed by treatment in everyone detected to have AKI or randomization to the intervention after screening with biomarker to detect AKI among all participants.\textsuperscript{63} Adaptive trial designs would permit multiple therapeutic-agent trials to be tested with an upfront prophylactic agent in combination with a separate therapeutic agent after detection of AKI with biomarkers.\textsuperscript{64} If predictive models become reliable enough to accurately risk stratify patients before surgery, these may also be used to optimize therapeutic trials in AKI.

**Ongoing Trials**

Advances in identifying individuals at risk for AKI early are of limited value if they cannot be used to meaningfully improve patient outcomes. To date, attempts to prevent and attenuate renal injury have met with limited success. Current renal protective strategies involve optimization of renal perfusion, avoidance of nephrotoxic agents, and the use of several pharmaceutical agents. Despite decades of trying to mitigate the severity of renal injury, none of these strategies have shown a consistent benefit in improving outcomes such as reduced incidence of AKI requiring dialysis or death.\textsuperscript{65-67} Are the traditional methods of renal protection truly ineffective, or are they simply implemented too late to have a meaningful effect? Will new discoveries regarding the importance of genetic susceptibility to AKI and advances in multimarker panels allow us to tailor therapies to individuals with varying genotypes, comorbid conditions, and types of renal injury (Figure 3)?

Although these biomarkers are still early in the process of being validated, several are likely to be used in clinical trials. Some current trials are revisiting previously tested renal protective agents whereas others are testing newer ones. Nonetheless, there are several exciting trials under way in post–cardiac surgical AKI. For example, erythropoietin has been shown to have diverse effects on nonhematopoietic tissues that may be beneficial in the prevention of AKI. One such effect is the attenuation of polymorphonuclear leukocyte priming, via direct action of erythropoietin on polymorphonuclear leukocytes to decrease systemic inflammation and oxidative stress.\textsuperscript{68} Evidence is also emerging of its cerebral and myocardial protective properties in ischemia–reperfusion injury.\textsuperscript{69} Several ongoing trials seek to determine whether erythropoietin has renal protective benefits as well: Effect of Erythropoietin in Kidney After Cardiac Surgery\textsuperscript{70} and Recombinant Human Erythropoietin
Use in Intensive Care Unit Patients: Does it Prevent Acute Renal Failure. In another study, patients are randomized to erythropoietin if they are found to have AKI postoperatively by an index of γ-glutamyl transpeptidase and alkaline phosphatase.

Another promising treatment currently under investigation for the prevention of AKI is minocycline. A second-generation tetracycline, this antibiotic has both anti-inflammatory and antiapoptotic properties. It has been shown in rat models to reduce nephogenic inflammation and cell death. Currently, there is a randomized, double-blind placebo control study under way to evaluate its efficacy preoperatively in patients with preexisting renal insufficiency undergoing cardiac surgery.

Intrarenal infusion of medication is another emerging therapy proposed to improve efficacy and decrease the systemic effects of renal protective therapies. For instance, although systemic administration of a vasodilator may be detrimental in a hypotensive postsurgical patient, selective renal vasodilation via intrarenal catheter infusion may be beneficial in preventing AKI. There have been many animal studies showing beneficial effects of intrarenal infusions on AKI, ranging from erythropoietin to calcium antagonists and acetylcholine. Continuous renal infusion of fenoldopam, a well-known vasodilator, was recently demonstrated to decrease the incidence of AKI by half (12.6% vs 27.6% in the placebo group). In addition, intrarenal fenoldopam has been used successfully in several case reports and a small pilot trial, but there are no trials to date in the cardiac surgery population.

In addition, other therapies being investigated or revisited in AKI post–cardiac surgery are sodium bicarbonate, N-acetylcysteine, and tight glucose control.

Summary and Future Directions

Acute kidney injury in the postoperative cardiac surgery population remains a significant cause of perioperative morbidity and mortality. Despite extensive research in the prediction and treatment of this disease, there has been limited success in altering patient outcomes. With advances in our understanding of underlying clinical and genetic risk, as well as the development of more sensitive and specific biomarkers, we appear to be on the cusp of a new era of AKI treatment. Once promising therapies are identified, customized approaches would harness information from individuals’ own genetic profiles and biomarker responses following cardiac surgery to identify specific personalized interventions. For example, preoperative evaluation may include a genetic panel that stratifies patients into categories of risk and targets them for preventive therapies. For some high-risk patients, this may also assist with the decision whether to proceed with surgery or to use more conservative medical management for their cardiovascular disease. During the perioperative period, urinary and serum biomarkers could be used to detect AKI in the earliest stages, confirm the appropriate phenotype warranting intervention, and discern anticipated responses to available agents to deliver tailored therapy to each individual patient. Although such a future hinges on many advances from the current state, we believe that this multifaceted, individualized approach will finally lead to meaningful improvements in postoperative AKI.

Acknowledgments

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References


Figure 1.
Proposed perioperative risk stratification of post–cardiac surgery acute kidney injury and management plan.
Figure 2.
Comparison of traditional “late” approach versus proposed biomarker “early” approach in the diagnosis post–cardiac surgery acute kidney injury.
Figure 3.
Using biomarkers to predict outcomes and target early interventions following acute kidney injury to improve outcomes.