Cardiopulmonary Bypass–associated Acute Kidney Injury

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Approximately 300,000 patients undergo cardiac surgical procedures each year in the United States. More than 80% of routine cardiac surgical procedures are performed using cardiopulmonary bypass (CPB).1 Acute kidney injury (AKI; previously referred to as acute renal failure) after CPB is a well-known, yet incompletely understood, entity that has significant implications on both short- and long-term outcomes. The development of AKI after CPB is associated with a significant increase in infectious complications, an increase in length of hospital stay, and greater mortality when compared with patients without AKI-CPB.2 The incidence of AKI-CPB averages 20–30%, depending on the definition used and the duration of the postoperative period studied.3,4 Furthermore, more patients with AKI-CPB who require dialysis remain dialysis dependant. For all patients undergoing CPB, the risk of AKI-CPB is the least in those who undergo coronary artery bypass grafting (CABG) only; the risk increases for patients undergoing valve replacement surgery; and the risk is the greatest after combined CABG-valve procedures.4 There has not been a significant reduction in mortality, despite many recent advances in our understanding of the causative pathophysiology and pharmacotherapeutics of AKI-CPB. Furthermore, advances in renal replacement therapies (RRTs) have not significantly altered the overall mortality associated with AKI-CPB.

In this review, we will focus on the current definitions of AKI, pathophysiologic features, and risk factors for developing AKI-CPB. We will also discuss perioperative strategies and emerging concepts that add to our understanding of this complex entity to help better manage patients at risk for AKI-CPB.

Defining AKI

AKI is a complex diagnosis and has been described using several definitions and diagnostic criteria, ranging from a 25% increase in baseline serum creatinine (sCr) to the need for hemodialysis.3,4 The requirement for a consensus definition addressing early detection and grading of severity of AKI led to the development of the Risk-Injury-Failure-Loss-End stage kidney disease (RIFLE) classification by the Acute Dialysis Quality Initiative.5 To further refine the scoring, the Acute Kidney Injury Network (AKIN) proposed a modification of the RIFLE classification, known as the AKIN classification.6 The RIFLE and AKIN classifications have been used and validated in prospective studies7 in patients with AKI after cardiac surgery.

The differences between RIFLE and AKIN staging criteria are subtle. Stage 1 in the AKIN classification has been broadened to include patients with an increase in sCr of at least 26.5 μM (0.3 mg/dl) greater than baseline because there is accumulating evidence that even minor increments in sCr concentration are associated with adverse outcomes.6 In contrast, the “risk” stage of RIFLE classification requires a 50% increase in sCr over baseline. Urine output over time is retained in both classification systems because it may precede the increase in sCr, especially in critically ill patients. The AKIN classification uses a 48-h window for assessment of renal function, whereas the RIFLE classification uses a 7-day window. The time constraint of 48 h was selected by AKIN based on evidence that adverse outcomes were reported when the creatinine elevation occurred within 24–48 h of hospitalization.6 Any patient treated with RRT, irrespective of urine output or sCr concentration, is categorized as having a stage 3 condition in the AKIN system. In contrast, the RIFLE system classifies patients receiving RRT under the “loss” or “ESKD” (end stage kidney disease) group, depending on the duration of RRT. The loss and ESKD classes are removed from the AKIN classification because they represent outcomes or long-term phases of the disease process, rather than the short-term processes.
Both classifications have limitations. Neither indicates the actual site of kidney injury (e.g., tubular or glomerular injury). In addition, both classifications rely heavily on sCr, which, by itself, is not an ideal biomarker for AKI. In general, there is no clear consensus regarding the advantage of RIFLE versus AKIN for patients with AKI-CPB. The diagnostic criteria for both systems are outlined in table 1.

**Pathogenesis of AKI-CPB**

The pathophysiologic features of AKI-CPB are complex and multifactorial. Reduced renal perfusion pressure, activation of proinflammatory mediators, and direct nephrotoxicity are central in the pathogenesis of AKI-CPB. CPB itself contributes to the pathogenesis via the systemic inflammatory response syndrome, sequelae of alterations in regional blood flow and vasomotor tone in the kidneys, and the generation of microemboli. CPB-associated systemic inflammatory response syndrome is triggered primarily by the contact of blood components with the artificial surface of the bypass circuit. Tumor necrosis factor (TNF) α, interleukin (IL) 6, and IL-8 are key cytokines implicated in the pathogenesis of AKI-CPB, but their precise role is not clear. Instituting CPB itself decreases the effective renal perfusion pressure up to 30% by altering the vasomotor tone and exposes the renal parenchyma to reduced oxygen tension, contributing to ischemia–reperfusion injury. CPB-induced erythrocyte hemolysis and activation of complement proteins further exacerbate CPB systemic inflammatory response syndrome and contribute to ischemia–reperfusion injury. Microemboli are formed during CPB and can be composed of combinations of fibrin, platelet aggregates, cellular debris, fat, and air. The CPB system can filter emboli larger than 40 μm; however, smaller emboli that are not effectively filtered can directly damage renal capillaries. Alternate pathophysiologic mechanisms have been proposed, including pigment nephropathy or sideropathy, in which free iron-related toxicity may play a role. The increased concentrations of free erythrocyte constituents (i.e., hemoglobin and iron) during CPB and subsequent exhaustion of their scavengers, such as transferrin and haptoglobin, can lead to alterations in systemic vascular resistance and platelet function and renal tubular damage.

The contribution of CPB to AKI-CPB itself is again highlighted by the decreased overall incidence of AKI in patients undergoing cardiac surgery by the off-pump technique.

**Identifying Patients at Risk for AKI-CPB**

Early identification of patients at risk for AKI-CPB is an important strategy to better care for patients during the perioperative period. At least five validated risk-predictive models of AKI-CPB have been developed. A list of the major risk factors described in the various risk-prediction models for AKI-CPB is given in table 2. These include some of the risk factors described in risk-prediction scores for non-cardiac surgery as well, including advanced age, preexisting kidney disease, diabetes mellitus, and chronic obstructive pulmonary disease. Increased preoperative sCr is by far the most important predictive risk factor for AKI-CPB. The risk of AKI requiring

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**TABLE 1. A Comparison of the RIFLE and AKIN Classification and Definitions for Acute Kidney Injury**

<table>
<thead>
<tr>
<th>RIFLE Criteria*</th>
<th>AKIN Criteria†</th>
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<tbody>
<tr>
<td><strong>Stage</strong></td>
<td><strong>GFR or Creatinine</strong></td>
</tr>
<tr>
<td>Risk</td>
<td>GFR decrease &gt; 25% or S Cr increase x 1.5 (baseline)</td>
</tr>
<tr>
<td>Injury</td>
<td>GFR decrease &gt; 50% or S Cr increase x 2 (baseline)</td>
</tr>
<tr>
<td>Failure</td>
<td>GFR decrease &gt; 75% or S Cr increase x 3 (baseline) or level of 4.0 mg/dl with an acute increase of 0.5 mg/dl</td>
</tr>
<tr>
<td>Loss</td>
<td>Persistent AKI = loss of renal function &gt; 4 weeks</td>
</tr>
<tr>
<td>ESKD</td>
<td>End stage kidney disease &gt; 3 months</td>
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* Renal assessment time window up to 7 days. † Renal assessment time window up to 48 h.

AKI = acute kidney injury; AKIN = Acute Kidney Injury Network; GFR = glomerular filtration rate; RIFLE = Risk-Injury-Failure-Loss; End stage kidney disease; RRT = renal replacement therapy; S Cr = serum creatinine; UO = urine output.
dialysis approaches 10–20% in patients with a baseline creatinine concentration of 2.0–4.0 mg/dl and approximately 25% when the baseline creatinine concentration is greater than 4.0 mg/dl. Other established patient-related major risk factors include female sex, left ventricular ejection fraction lower than 40%, diabetes mellitus, preoperative use of an intraaortic balloon pump, and the need for emergency surgery. Interestingly, most of the patient-related factors are modifiable only to a marginal extent, if at all.12–17

Among surgical risk factors, valve procedures are associated with a higher risk compared with CABG alone; the risk for AKI-CPB is the highest for combined CABG-valve procedures. Emergency surgery and a low cardiac output state, requiring inotropic/device support during the perioperative period, carry an increased risk of AKI-CPB.4,19 The ability to accurately predict AKI-CPB provides an opportunity to develop strategies for early diagnosis and treatment.

**Perioperative Management of AKI-CPB**

The major preoperative goals include correcting intravascular volume depletion, optimizing cardiac output, and providing congestive heart failure therapy before surgery. Nephrotoxic agents, such as nonsteroidal antiinflammatory drugs, should be discontinued and exposure to radiocontrast agents should be avoided or minimized. Whether angiotensin converting enzyme inhibitors and angiotensin receptor blocker should be discontinued before surgery to reduce AKI-CPB is still debatable.20

The intraoperative period is likely the phase during which most of the modifiable risk factors can be optimized. Maintaining adequate tissue perfusion is the primary goal when instituting CPB and is achieved by modulating the mean arterial pressure (MAP) and CPB flow rates during bypass. The most commonly used range for the CPB flow rate is between 2.2 and 2.5 l/min m⁻² (i.e., flow to match the cardiac index in a normothermic adult with normal hemoglobin and hematocrit concentrations). Most centers use an MAP range between 50 and 70 mmHg for CPB. There is insufficient evidence to suggest minimum flow rates or MAP parameters for patients undergoing CPB to specifically prevent renal injury.21 Theoretically, hemodilution during CPB may improve organ perfusion by decreasing blood viscosity and improving microcirculatory flow. However, four recent studies22–25 have demonstrated a significant increase in the incidence of AKI when the hematocrit during CPB decreased lower than the 21–24% range. Based on current evidence, the blood conservation guidelines published by the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists suggest maintaining a hematocrit of at least 21% (hemoglobin concentration, 7 g/dL) during CPB.26

Evidence supports an independent association between the duration of CPB and the development of AKI-CPB.27 In general, the longer the duration of extracorporeal support, the higher the risk of coagulopathy, the need for transfusion support, gut hypoperfusion, and AKI.28 There is no single defined threshold time during CPB beyond which the incidence of AKI increases dramatically. Future studies may better define a “safe time window” during CPB to decrease AKI-CPB.

There has been a renewed focus on glycemic control and outcomes after a landmark intensive care unit study29 showed significantly improved outcomes with tight glucose control (defined as a blood glucose concentration of 80–110 mg/dL). However, at least two recent randomized controlled trials in patients undergoing cardiac surgery found an increased risk of adverse outcomes when intraoperative glucose concentrations were actively titrated toward normoglycemia.30 Severe intraoperative and early postoperative hyperglycemia (glucose concentration more than 200 mg/dL) and glucose variability (measured as the coefficient of variation) during the postoperative period were stronger predictors of worsening (including renal) outcomes, rather than tight glucose control. Emerging evidence points toward maintaining perioperative blood glucose concentrations lower than 180 mg/dL while avoiding large fluctuations in blood glucose, rather than trying to achieve blood glucose concentrations suggested by the tight glucose control strategy.30

Several pharmacologic and therapeutic approaches have been used in an attempt to decrease the incidence of AKI-CPB during the postoperative period. Although some of these interventions appear promising in early studies, conclusive evidence to support their widespread use is lacking. The role of recombinant cardiac natriuretic peptides is being revisited after the encouraging results of recent trials. Atrial natriuretic peptide induces natriuresis by increasing the glomerular filtration rate and inhibiting sodium reabsorption in the collecting ducts. In a recent trial, the use of low-dose atrial natriuretic peptide significantly decreased the need for dialysis after CPB in patients with decompensated congestive heart failure and improved dialysis-free survival at 21 days.31 Nesiritide (recombinant human β natriuretic peptide) is another cardiac natriuretic peptide that produces diuresis and natriuresis while maintaining renal blood flow. The results of

### Table 2. Major Risk Factors for Developing AKI-CPB

<table>
<thead>
<tr>
<th>Patient Factors</th>
<th>Surgical Factors</th>
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<tbody>
<tr>
<td>Age</td>
<td>Hemodilution on CPB</td>
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<tr>
<td>Female gender</td>
<td>Intraaortic balloon pump use</td>
</tr>
<tr>
<td>Preoperative renal insufficiency</td>
<td>Valve surgery and combined valve-CABG procedures</td>
</tr>
<tr>
<td>EF &lt; 40%</td>
<td>CPB duration</td>
</tr>
<tr>
<td>Emergency surgery</td>
<td></td>
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<tr>
<td>Diabetes mellitus</td>
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AKI = acute kidney injury; CPB = cardiopulmonary bypass; EF = ejection fraction.
the Nesiritide Administered Per-Anesthesia in Patients Undergoing Cardiac Surgery trial demonstrated short-term benefits of nesiritide on perioperative renal function, as assessed by attenuating the increase in sCr, and maintained glomerular filtration rate and greater urine output 24 h after surgery.32 Although a beneficial effect of low-dose atrial natriuretic peptide and nesiritide is suggested, there are insufficient data to recommend natriuretics in all patient populations.

Drugs that increase renal perfusion provide another intervention strategy to prevent AKI-CPB. Several agents have been tested. Fenoldopam, a selective dopaminergic receptor 1 agonist, reduced the incidence of AKI-CPB in small nonrandomized or uncontrolled trials.33 The benefits of renal vasodilation may be offset by systemic hypotension that can occur with the use of fenoldopam. Innovative approaches using catheter-based infusion of fenoldopam directly into the renal vessels are being investigated.34 Further adequately powered studies are warranted before broad recommendations can be made.

An alternate pharmacologic strategy is to inhibit CPB-induced inflammation and oxidative stress using N-acetylcysteine. However, several recent studies and summaries using meta-analyses failed to demonstrate a protective benefit of N-acetylcysteine in preventing AKI-CPB. Its routine use cannot be recommended.35

Diuretics remain among the most widely used class of drugs for managing global fluid volume status during the immediate postoperative period. Diuretics theoretically reduce the severity of AKI by preventing renal tubule obstruction (by increasing urine output) and decreasing oxygen consumption in the cells lining the renal tubules. However, clinical outcome studies36 do not support the routine use of aggressive diuresis (including diuretic infusions) in the immediate postoperative period to reduce AKI-CPB. Similarly, the role of low-dose dopamine (1–3 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \)) to improve renal perfusion has been extensively debated over the years. Numerous studies37 have failed to show its efficacy in preventing AKI-CPB. Based on current evidence, there is no role for the use of dopamine or aggressive diuretic therapy in the treatment or prevention of AKI-CPB.

Prophylactic RRT as a therapeutic option in high-risk patients set to undergo CPB is another strategy that has been considered. Previous studies managing AKI-CPB with prophylactic RRT have been limited by the lack of consistent RRT initiation criteria, whereas several other single-center studies have not been adequately powered to determine the outcomes of AKI-CPB.38 Prophylactic RRT may become a viable option in the future, with the standardization of RRT initiation criteria backed by larger clinical trials. An overview of the pathophysiologic mechanisms and management strategies for preventing AKI-CPB is outlined in figure 1.

**Alternate Strategies in Management**

Alternate surgical approaches that minimize and/or avoid CPB have been studied extensively. The 1990s saw the dev
development of “off-pump” or “beating heart” surgical techniques for cardiac surgery. This technique allows maintenance of pulsatile flow and allows no exposure to an extracorporeal circuit, with an anticipated reduction in the inflammatory cytokine response. Most early studies that tried to address the advantage of the off-pump technique versus “on-pump” surgery lacked randomization, were single-center studies, and were limited by a heterogeneous patient population with different baseline risks of developing AKI. Despite these inherent weaknesses, most available data support a decreased risk of AKI associated with off-pump surgical procedures. In fact, the American Heart Association released a position statement on decreased renal risk with the off-pump technique compared with traditional CPB-based surgery.10

There is increasing interest in miniature CPB systems that promise the convenience of on-pump surgery while minimizing the disadvantages of conventional CPB. Miniature CPB systems use heparinized tubing and oxygenators, decrease pump prime volumes, and eliminate cardiotoxic suction and venous reservoirs. The elimination of a venous reservoir in the closed-loop miniature CPB offers a potentially greater intravascular volume and an increased MAP compared with conventional CPB. The limited hemodilution with miniature CPB systems may account for the reduction in postoperative erythrocyte transfusion requirements. Together, these effects may be directly and indirectly renoprotective.39

Surgical technique should be based on careful patient selection, the individual surgeon’s experience, and the surgical experience of the particular medical center.

Early Detection of AKI: The Emerging Role of Biomarkers in AKI-CPB

sCr remains the most frequently used parameter in the diagnosis of AKI. sCr is an insensitive and unreliable biomarker during short-term changes in kidney function because it lags behind the decline and recovery in glomerular filtration rate by days. Moreover, sCr is affected by age, race, muscle mass, volume of distribution, medications, and protein intake; it does not discriminate the nature of renal insult (e.g., ischemic vs. prerenal insult). Therefore, there is a need for more sensitive and specific biomarkers that can diagnose AKI earlier, possibly indicate the cause, and rapidly measure the response to therapy.

In 2005, the American Society of Nephrology designated the identification and characterization of biomarkers for AKI as a key research area.40 This has led to the identification and evaluation of more than 20 unique biomarkers of AKI. The performance of a biomarker is usually reported as the area under the receiver-operating characteristic curve (AUCROC). Biomarkers have a good discriminatory value if the AUC is greater than 0.75 and an excellent discriminatory value if the AUC is greater than 0.90.41 We will briefly discuss biomarkers with emphasis on those most likely to be available in clinical practice over the next 1 to 2 yr.

Neutrophil gelatinase-associated lipocalin (NGAL) has generated the greatest interest as a biomarker for the diagnosis of AKI-CPB. In patients with normal kidney function, NGAL concentrations are almost undetectable in either plasma or urine. However, with sudden tubular injury, NGAL is increased in both urine and plasma. NGAL is a sensitive and specific marker for AKI-CPB in pediatric patients undergoing cardiac surgery. This diagnostic characteristic in adult patients undergoing cardiac surgery has been less consistent and the reason for the discrepancy is not clear.41,42 In pediatric and adult patients after CPB cardiac surgery, the 2-h post-CPB NGAL concentration of 150 ng/ml for the prediction of AKI-CPB has an AUCROC of 0.96, a sensitivity of 84%, and a specificity of 94%. The plasma 2-h post-CPB NGAL concentration strongly correlated with the severity and duration of AKI and the length of hospital stay. In addition, the 12-h plasma NGAL strongly correlated with mortality.41,40

A 2-h post-CPB urine NGAL greater than 100 ng/ml predicts AKI-CPB (AUCROC, 0.95; sensitivity, 82%; specificity, 90%). The 2-h urine NGAL concentration correlated with severity and duration of AKI, length of stay, dialysis requirement, and death.41 It is not known how other comorbidities affect NGAL concentrations. Further studies in specific patient populations are needed before this biomarker can be widely used.

Several other candidate biomarkers have been identified, including cystatin C, kidney injury molecule-1, IL-18, and others. Cystatin C is a potential marker for glomerular filtration rate. It also appears to be independent of age, sex, and lean muscle mass. Because of mixed results in early studies, its precise value in the diagnosis and prognosis of AKI-CPB is unclear.40 Kidney injury molecule-1, like NGAL, is usually undetectable in the urine of patients with normal kidney function. Kidney injury molecule-1 is markedly up-regulated in the proximal tubule after an acute ischemic insult. Early studies40 showed a poor sensitivity (lower than 50%) in patients with AKI-CPB; therefore, its utility in the diagnosis and management of CPB-AKI has not been validated. Acute tubular injury secondary to a variety of causes, including AKI-CPB, results in a significant increase in urinary concentrations of IL-18. Urinary IL-18 concentrations appear to correlate better with the duration of CPB in adults than AKI-CPB itself, suggesting that IL-18 may be a marker of inflammation rather than a marker of specific kidney injury in those undergoing CPB.40 Measurements combining different biomarkers may improve the detection of AKI-CPB. There are insufficient data to make recommendations regarding the combinations of biomarkers to be used in the early diagnosis and management of AKI-CPB.40 Despite the enthusiasm with novel biomarkers, most of them are still not available for routine clinical practice. Many of the early studies have reported wide variations in diagnostic characteristics,
and confounders for the various individual biomarkers are not well understood. Early studies for evaluating biomarkers also excluded patients with preexisting kidney disease, a high-risk group for AKI-CPB and a group in whom early diagnosis and stratification of disease are key. Results of future adequately powered studies that meet the Standards for the Reporting of Diagnostic accuracy studies reporting standards are anticipated.

Conclusion

The unacceptably high morbidity and mortality of AKI-CPB, despite the advent of RRT and intensive care unit care, highlight the importance of this problem. Perioperative management strategies include identifying high-risk patients, optimizing cardiac output and renal perfusion pressure, and avoiding nephrotoxins. Using the off-pump surgical technique when applicable or minimizing the time undergoing CPB may also help improve the overall incidence of AKI-CPB. In the future, early detection and determination of cause may be improved by using biomarkers. Finally, understanding CPB-induced inflammation and cell damage, modulating the inflammatory pathways, and improving CPB technology may reduce the incidence and severity of AKI-CPB.

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