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Review Articles

Novel Biomarkers for Cardiac Surgery-Associated Acute Kidney Injury: A Skeptical Assessment of Their Role

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Abstract: Cardiac surgery-associated acute kidney injury (AKI) is common and is associated with a high mortality rate. Traditional biomarkers of AKI (creatinine and urea) increase slowly in response to renal injury, are insensitive to mild degrees of AKI, and are influenced by nonrenal factors. There is considerable interest in novel biomarkers of AKI such as neutrophil gelatinase-associated lipocalin that increase rapidly after renal injury, detect mild degrees of AKI, and are less subject to nonrenal factors. It has been postulated that the early diagnosis of cardiac surgery-associated AKI using novel biomarkers will result in improved outcomes. However, there is little evidence that interventions started early in the course of evolving AKI enhance renal recovery. Until effective therapies are developed that significantly improve the outcome from AKI, there is little benefit from early diagnosis using novel biomarkers.
Keywords: acute kidney injury, cardiac surgery, postoperative care, risk factors, biological markers, complications. *JECT. 2012;44:235–240*

Cardiac surgery-associated acute kidney injury (AKI) is common. However, until recently, lack of robust definitions has made it difficult to compare incidences and outcomes between different populations. In 2004, the Acute Dialysis Quality Initiative (ADQI) developed the RIFLE criteria for categorizing AKI based on urine output and changes in serum creatinine and glomerular filtration rate (GFR) relative to baseline (Table 1) (1). In 2007 the RIFLE criteria were simplified by the Acute Kidney Injury Network (AKIN) to include three stages of AKI (AKIN Grades I, II, and III) based on urine output and changes in serum creatinine relative to baseline (Table 2) (2). The RIFLE and, later, the AKIN criteria have been widely adopted by clinicians and researchers and provide a useful way of comparing rates of AKI between different populations. Using these criteria, the incidence of AKI after cardiac surgery is 20–30% (3–5). Approximately 2–3% of patients require postoperative renal replacement therapy (RRT) (6).

Mortality associated with AKI is directly related to the severity of the kidney injury, being over 40% in patients requiring RRT (6,7). Even mild forms of AKI are associated with significantly increased mortality (3,4,8). In one study, a postoperative creatinine rise of less than .5 mg/dL (<45 μmol/L) was associated with a threefold increased mortality rate (9).

Novel biomarkers offer significant advantages compared with conventional tests of kidney function: they are less influenced by nonrenal factors such as muscle mass and metabolic rate, detect minor degrees of renal impairment, and increase rapidly in response to kidney injury, much earlier than creatinine.

The argument in favor of using novel biomarkers is based on two assumptions. First, earlier diagnosis allows earlier initiation of treatment to prevent or reduce the severity of AKI. Second, reducing the severity of AKI may lead to improved mortality. It is uncertain, at least to this author, that either assumption is correct.

Regarding the second assumption, although cardiac surgery-associated AKI is directly related to mortality,

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Table 1. RIFLE criteria for acute kidney injury.

Stage	Creatinine/GFR	Urine Output
Risk	Increased × 1.5 above baseline or GFR decreased > 25%	<.5 mL/kg/h × 6 hours
Injury	Increased × 2 above baseline or GFR decreased > 50%	<.5 mL/kg/h × 12 hours
Failure	Increased × 3 or >4 mg/dL (>350 μmol/L) with acute rise > .5 mg/dL (>45 μmol/L) or GFR decreased > 75%	<.3 mL/kg/h × 24 hours or anuria × 12 hours
Loss	Persistent acute renal failure > 4 weeks	
ESRD	Complete loss of kidney function for >3 months	

GFR, glomerular filtration rate; ESRD, end-stage renal disease.

Table 2. AKIN criteria for acute kidney injury.

Stage	Creatinine	Urine Output
I	Increased × 1.5 above baseline or >.3 mg/dL (>25 μmol/L)	<.5 mL/kg/h × 6 hours
II	Increased × 2 above baseline	<.5 mL/kg/h × 12 hours
III	Increased × 3 or >4 mg/dL (>350 μmol/L) with acute rise > .5 mg/dL (>45 μmol/L)	<.3 mL/kg/h × 24 hours or anuria × 12 hours

it does not necessarily follow that reducing the former reduces the latter. The association between AKI and mortality has been derived from nonrandomized series (3,4,8,9), in which, despite appropriate statistical testing and case matching, an unequivocal cause-and-effect relationship between AKI and mortality has not been established. It is possible, likely even, that the cause of increased mortality is nonrenal perioperative risk factors (e.g., low ejection fraction, complex surgery, etc.), which also increase the risk of developing postoperative AKI.

Addressing the first assumption, that AKI can be ameliorated or prevented by earlier diagnosis, is the primary focus of this article.

Biochemical Tests of Acute Kidney Injury

Standard tests of kidney function assess either GFR or tubular function. Creatinine, the most widely used marker of kidney function, is released from skeletal muscle at a fairly constant rate, is freely filtered by the glomerulus, and, unlike urea, does not undergo tubular reabsorption. Creatinine does, however, undergo tubular secretion, which accounts for 10–40% of creatinine clearance. There are several limitations of using creatinine as a measure of GFR. GFR must decline by approximately 50% before creatinine increases significantly. Thus, a rise in creatinine from 50–100 μmol/L represents a greater proportional reduction in GFR than a rise from 200–300 μmol/L. Serum creatinine is influenced by body size, muscle mass, protein intake, gender, volume of distribution (i.e., dilution effect), and catabolic state. In older patients, reduced muscle mass is matched by reduced GFR, resulting in little change in serum creatinine. Thus, creatinine does not "capture" age-related decline in GFR. Finally, and crucially, creatinine rise is delayed 48–72 hours from the initiation of renal injury.

Urea, a byproduct of protein metabolism, is freely filtered at the glomerulus and, unlike creatinine, undergoes tubular reabsorption. Urea production is not stable, changing with protein intake and metabolic state and increasing significantly with gastrointestinal bleeding. Urea increases earlier than creatinine in response to renal injury.

Several empiric formulae are available for estimating GFR based on serum creatinine, age, weight, and gender (10,11). These formulae are well validated for diagnosing and quantifying chronic kidney disease, albeit with limitations within specific patient populations (e.g., the obese and the elderly), and are therefore very useful for assessing renal function in stable patients preoperatively. However, these formulae are not valid in patients with oliguria or unstable kidney function and have no role in patients with evolving AKI (12).

Several tests of tubular function exist, of which urinary osmolality, urinary sodium, and fractional excretion of sodium are the most widely used. However, these tests are invalidated by diuretic use and have limited use in postoperative cardiac surgical patients.

Because of the limitations of existing tests of kidney function, there is considerable interest in novel biomarkers of AKI (13–15). Biomarkers that have been investigated include cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), and liver-type fatty acid binding protein (L-FABP).

Novel biomarkers are either physiologic or pathologic (13,14). Physiologic biomarkers are substances normally released from cells and excreted by the kidney. Creatinine, urea, and cystatin C are physiologic biomarkers. By contrast, pathologic biomarkers are substances that are expressed in response to kidney injury. NGAL, KIM-1, IL-18, and L-FABP are all pathologic biomarkers. NGAL, KIM-1, and IL-18 are immunological proteins, whereas L-FABP is a fatty-acid binding and transport protein found in the proximal renal tubule. The expression of all four substances is dramatically increased by tubular injury.

NGAL is the most widely investigated and promising of the novel biomarkers. NGAL is normally present in neutrophils and tubular epithelial cells where it functions as an antioxidant. NGAL increases early, within 2 hours, of renal injury and has been shown to be predictive of the duration and severity of AKI and the need for RRT (16–18). NGAL has been assessed in cardiac surgical patients. In one study of pediatric patients, urinary NGAL

greater than 50 μg/L 2 hours after surgery predicted the risk of AKI with a sensitivity of 100% and a specificity of 98% (19). By contrast, rises in serum creatinine did not occur until 1–3 days postsurgery. Similar, although slightly less impressive, results have also been obtained in adult cardiac surgical patients (16,18). A limitation of NGAL is that higher cutoff values for diagnosing AKI are required in adults compared with children and in cardiac surgery-associated AKI compared with contrast-induced nephropathy (13). Thus, several different normal ranges are required depending on the clinical scenario. Furthermore, cardiopulmonary bypass (CPB) per se appears to increase urinary NGAL levels independent of AKI (20), which may limit its use in cardiac surgery patients. Further studies are needed to clarify the role of NGAL in diagnosing cardiac surgery-associated AKI.

Cystatin C, a protein released from nucleated cells, is a physiologic marker similar to creatinine (13). Cystatin C is freely filtered by the glomerulus and is virtually completely reabsorbed and catabolized in the proximal tubule; it does not undergo tubular secretion. Plasma and urinary concentrations of cystatin C reflect changes in GFR and tubular function. Cystatin C increases within 12 hours of the initiation of AKI; i.e., later than NGAL (13).

Pathophysiology of Acute Kidney Injury

Previously, the terms prerenal azotemia, meaning elevated levels of nitrogen wastes in the blood, and acute tubular necrosis were used to describe the early and late phases of AKI (21). However, these terms do not define distinct clinical entities and are no longer favored. The ADQI and AKIN groups prefer the concept of volume-responsive AKI to describe the early, potentially reversible form of AKI and nonvolume-responsive AKI to describe the later stages of AKI (21,22). Volume-responsive AKI describes a condition of reduced GFR resulting from renal hypoperfusion without histopathological changes within the kidney. Volume-responsive AKI is characterized by a series of adaptive physiological responses including tubuloglomerular feedback, renin release by the kidney, aldosterone release by the adrenal gland, and vasopressin release by the posterior pituitary. Collectively, these mechanisms help to restore renal blood flow and GFR and result in the production of a low-volume, concentrated, salt-poor urine. These changes represent the normal physiological response to reduced renal perfusion pressure and, within limits, can be reversed by volume administration.

However, a sustained fall in renal blood flow leads to histopathological changes in the renal microvasculature and tubules resulting from ischemia and inflammation, which is not reversible by restoration of circulating volume. Nonvolume-responsive AKI is characterized by a progressive fall in GFR, an inability to generate concentrated urine, and reduced tubular reabsorption of sodium. The serum concentration of substances dependent on filtration and tubular secretion such as potassium, hydrogen ions, and phosphate all increase. Urinary sodium losses increase and oliguria progresses to anuria.

Although the concept of volume-responsive AKI provides a useful framework for understanding the early phase of AKI as a result of reduced renal perfusion pressure, and signals an obvious therapeutic intervention, it is less useful for AKI associated with cardiac surgery. The pathogenesis of cardiac surgery-associated AKI is complex and involves exogenous and endogenous toxins, ischemia–reperfusion, neurohumoral activation, inflammation, and oxidative stress (23,24), much of which arises directly from the effects of CPB. Important etiologic factors of cardiac surgery-related AKI include impaired autoregulation during CPB (25), nonpulsatile flow during CPB (26), CBP-induced systemic inflammation, hemolysis (27), anemia (28,29), blood transfusion (30), and reduced tissue oxygen delivery (31). Only rarely is hypovolemia a primary cause of cardiac surgery-associated AKI.

Risk Factors and Prevention of Cardiac Surgery-Associated Acute Kidney Injury

Risk factors for cardiac surgery-associated AKI are listed in Table 3. Of these, by far the most important is preexisting renal impairment. In a cohort of over 10,000 cardiac surgical patients, a preoperative GFR of 30–60 mL/min was associated with an odds ratio of requiring RRT of 3.58 (95% confidence interval [CI], 2.45–5.26), whereas a GFR less than 30 mL/min was associated with an odds ratio of requiring RRT of 16.35 (95% CI, 9.34–28.02) (6).

Unsurprisingly, given the effects of CPB per se, prolonged CPB is an important risk factor for postoperative AKI (32). Both anemia and blood transfusion are associated with AKI. With respect to anemia, a hematocrit less than .24 during CPB is associated with an increased likelihood of developing AKI (28,29). The association between blood transfusion and AKI is significantly greater in anemic patients than in nonanemic patients (30). Thus, strategies to minimize both anemia and blood transfusion are likely to be beneficial. Such strategies include correcting anemia preoperatively, minimizing fluid administration during surgery, using autologous retrograde priming of the circuit, using small-volume circuits, using cell-saving devices, and administering an antifibrinolytic such as tranexamic acid (not aprotinin). If blood transfusion is necessary, avoiding overtransfusion (i.e., avoiding a hemoglobin concentration >90 g/L), and using fresh (<14 days old), leukocyte-depleted blood may be beneficial (33–35). Related to the issue of anemia is oxygen delivery during CPB. Ranucci and colleagues have demonstrated that an oxygen delivery of less than 272 mL/min/m^2 is an independent predictor of postoperative AKI (31,36). Interestingly, this group found that low hematocrit was also

Table 3. Factors associated with acute kidney injury during cardiac surgery.

Preoperative
Pre-existing renal dysfunction
ACEi/ARB therapy
Heart failure
Diabetes mellitus
Age > 70 years
Systolic hypertension (>140 mmHg) and wide pulse pressure (>40 mmHg)
Inotrope administration preoperatively
Hepatic disease
Intraoperative
Anemia/hemodilution
Blood transfusion
Reduced tissue oxygen delivery
Hemodynamic instability
Prolonged CPB (>2–3 hours)
On-pump CABG (vs. off-pump CABG)
Valvular or aortic surgery (vs. CABG surgery)
Use of multiple inotropic drugs
Use of IABP
Use of aprotinin
Postoperative
Hypotension
Sepsis
Use of aminoglycosides or vancomycin
Prolonged mechanical ventilation
High illness severity score
Use of IABP
Use of multiple inotropic drugs

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CPB, cardiopulmonary bypass; CABG, coronary artery bypass graft; IAPB, intra-aortic balloon pump.

a predictor of postoperative AKI but not so when corrected for the need for blood transfusion (31). This makes intuitive sense given that both anemia and transfusion are potentially harmful. A logical conclusion from these data is that higher pump flows may be beneficial in ameliorating postoperative AKI in anemic patients. Further data are required before this recommendation can be considered robust.

Preoperative systolic hypertension (>140 mmHg), particularly if associated with a wide pulse pressure (>40 mmHg), is associated with postoperative AKI (37–39). By contrast, diastolic hypertension (>90 mmHg) is not a risk factor. Labile blood pressure during the perioperative period is also associated with an increased risk of developing AKI (40). However, it is not known whether attempts to treat hypertension preoperatively or minimize blood pressure lability intraoperatively reduce AKI.

The relationship between mean arterial pressure (MAP) during CPB and postoperative AKI has been investigated in several small trials (35,41–43). Unfortunately, these studies are underpowered and provide conflicting results. One recent study demonstrated a strong association between hypotension (MAP < 50 mmHg) during CPB and postoperative AKI in anemic but not in nonanemic patients (35).

There are no data demonstrating a benefit of one type of resuscitation fluid or vasoactive drug over another for preventing AKI, specifically in cardiac surgical patients. However, recently the large multicenter randomized crystalloid versus hydroxyethyl starch trial (CHEST) study was published (44), in which 6651 patients admitted to intensive care units were randomized to receive fluid resuscitation with either .9% saline or 6% hydroxyethyl starch (Voluven; Fresenius, Bad Homburg, Germany), a commonly used artificial colloid. Although there was no difference in mortality, the need for RRT was significantly higher in the starch group. Although the study specifically excluded cardiac surgical patients, it does raise concerns regarding the use of artificial starches for volume resuscitation in critically ill patients. Additionally, other colloids, notably 20–25% albumin and high-molecular-weight hydroxyethyl starch (e.g., 10% pentastarch), are potentially nephrotoxic and should probably be avoided in patients at risk of AKI (12).

Optimal glucose management during cardiac surgery is controversial. There are limited data from small randomized trials and case series that tight perioperative glucose control (e.g., targeting a blood glucose of 80–110 mg/dL [4.5–6.1 mmol/L]) improves renal (45) and other outcomes (46). Countered against this is the fact that tight glycemic control increases the risk of hypoglycemia (47), and in a large multicenter randomized trial conducted in intensive care unit patients, there was no benefit for tight glucose control compared with targeting a blood glucose of less than 180 mg/dL (10 mmol/L) (48).

Some authors recommend performing coronary artery bypass graft surgery off-pump to reduce the risk of postoperative AKI. A recent meta-analysis demonstrated a protective effect for off-pump surgery in data obtained from observational studies, but data from randomized trials were insufficient to reach a consensus recommendation (49). By comparison, a recent large observational study involving over 14,000 patients demonstrated worse survival in patients with moderate or severe renal dysfunction undergoing off-pump surgery compared with on-pump surgery (50).

What Is the Role for Early Diagnosis of Postoperative Acute Kidney Injury Using Novel Biomarkers?

Based on the foregoing discussion, it is clearly possible to identify patients preoperatively who are at increased risk of developing postoperative AKI. In particular, patients with chronic kidney disease are at increased risk. However, chronic kidney disease is easily diagnosed using traditional tests of renal function with little additional benefit provided from novel biomarkers. Preoperative identification of high-risk patients allows strategies to be used that may ameliorate postoperative renal injury; for instance, preoperative correction of anemia and intraoperative use of blood conservation techniques to

reduce transfusion requirements, although the evidence in favor of any single strategy is modest.

One specific situation in which there may be a benefit for using novel biomarkers is in patients who have evolving AKI before planned surgery; for instance, as a consequence of acute heart failure or exposure to radiocontrast agents. In this circumstance, early diagnosis of AKI may trigger a decision to delay cardiac surgery until renal function has recovered. However, in many such instances, it may not be safe or appropriate to delay surgery.

Because novel biomarkers provide an early warning of evolving AKI, the question arises: does early diagnosis during the postoperative period allow initiation of therapies to reduce the severity of AKI? Unfortunately, there are few strategies to mitigate evolving AKI over and above that provided by standard postoperative care.

Prompt treatment of hypovolemia and hypotension is likely to be beneficial. Data from a recent meta-analysis of randomized trials involving high-risk, noncardiac surgical patients indicate that "goal-directed therapy" ameliorates AKI (51). However, as noted, in contrast to other patient groups, hypovolemia and hypotension are not important causes of cardiac surgery-associated AKI. Thus, augmenting cardiac output and blood pressure to supranormal levels is unlikely to mitigate cardiac surgery-associated AKI, although there are no randomized trial data to definitively answer this question.

Although nephrotoxins such as gentamicin and radiocontrast agents should be avoided in patients with evolving AKI, these agents should, if possible, be avoided as a matter of course in all patients at increased risk of AKI. A potential of benefit of early identification of evolving AKI would be to intervene with nephroprotective pharmacotherapy. Numerous drugs have been studied for their potential to ameliorate cardiac surgery-associated AKI, including dopamine, frusemide, nesiritide (B-type natriuretic peptide), fenoldopam, diltiazem, N-acetylcysteine, atrial natriuretic peptide, sodium bicarbonate, statins, and corticosteroids (52,53). There are limited, but conflicting, data supporting a nephroprotective effect for fenoldopam, atrial natriuretic peptide, and nesiritide. Thus, until definitive trial data are forthcoming, the role of nephroprotective agents remains uncertain.

A final, and somewhat obvious, point is that the early diagnosis of evolving AKI has no impact on the use of RRT, which is indicated by the fluid and metabolic consequences of AKI (54), not a predetermined rise in renal biomarker.

CONCLUSIONS

Traditional tests of kidney function such as creatinine and urea remain useful for assessing the preoperative risk of developing AKI after cardiac surgery and, as such, allow treatments to be instituted during the operative period that may ameliorate the severity of postoperative kidney injury. Although there is little doubt that novel biomarkers afford earlier diagnosis of evolving AKI than traditional tests, until effective treatments become available that target evolving AKI during the early postoperative period (i.e., effective nephroprotective agents), their use provides little additional benefit compared with traditional tests. Thus, it is unsurprising that current guidelines on diagnosing, preventing, and treating AKI in the critically ill continue to recommend serum creatinine, in association with urine output, as the primary test for assessing patients with evolving AKI (12).

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