Review Article

Cardiac surgery-associated acute kidney injury

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ABSTRACT

Cardiac surgery-associated acute kidney injury (CSA-AKI) is a well-recognized complication resulting with the higher morbid-mortality after cardiac surgery. In its most severe form, it increases the odds ratio of operative mortality 3–8-fold, length of stay in the Intensive Care Unit and hospital, and costs of care. Early diagnosis is critical for an optimal treatment of this complication. Just as the identification and correction of preoperative risk factors, the use of prophylactic measures during and after surgery to optimize renal function is essential to improve postoperative morbidity and mortality of these patients. Cardiopulmonary bypass produces an increased in tubular damage markers. Their measurement may be the most sensitive means of early detection of AKI because serum creatinine changes occur 48 h to 7 days after the original insult. Tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein 7 are most promising as an early diagnostic tool. However, the ideal noninvasive, specific, sensitive, reproducible biomarker for the detection of AKI within 24 h is still not found. This article provides a review of the different perspectives of the CSA-AKI, including pathogenesis, risk factors, diagnosis, biomarkers, classification, postoperative management, and treatment. We searched the electronic databases, MEDLINE, PubMed, EMBASE using search terms relevant including pathogenesis, risk factors, diagnosis, biomarkers, classification, postoperative management, and treatment, in order to provide an exhaustive review of the different perspectives of the CSA-AKI.

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INTRODUCTION

Acute kidney injury (AKI) is a long-recognized complication of cardiac surgery and the strongest risk factor for death in patients undergoing cardiac surgery. It is a commonly encountered clinical syndrome that, in its most severe form, increases the odds ratio of operative mortality 3–8-fold, length of stay in the Intensive Care Unit (ICU) and hospital, and costs of care.[1,2] Perioperative renal dysfunction is a major determinant of both operative and long-term mortality, following cardiac surgery.[3-6] Even patients with mild renal dysfunction before surgery are more likely to experience AKI with a compromised outcome.[7,8] It is essential to early recognize high-risk patients for developing postoperative AKI to give the appropriate support. This includes judicious fluid management, appropriate hemodynamic support, adjunctive pharmacologic therapy, or early aggressive use of renal replacement therapy (RRT).

ACUTE KIDNEY INJURY CONCEPT

For decades, there was no standard definition or staging system for the diagnosis of AKI and more than thirty different arbitrary definitions were used over time.[9] In 2004, Bellomo *et al*. introduced the RIFLE classification, which defined and staged renal failure over 7 days into five classes of increasing severity: Risk, injury, failure, loss, and end-stage kidney

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disease.[9] The first stage of AKI is currently defined as a reduction in estimated glomerular filtration rate (GFR) of >25%.

A revised revision of the RIFLE criteria was suggested by the Acute Kidney Injury Network (AKIN) group in 2007. It introduces 4 main changes: (i) GFR was omitted from the definition system, (ii) period of 7 days for serum creatinine (SCr) changes replaced by 48 h, (iii) SCr changes as low as 0.3 mg/dL is the lowest measure considered as AKI, and (iv) two last RIFLE stages (loss and end-stage) are deleted.[10] Studies have shown concerns about the adequacy of the AKIN and RIFLE criteria. An agreed consensus definition was necessary to improve the consistency of studies. The Kidney Disease Improving Global Outcome (KDIGO) workshop proposes a new definition. AKI is defined when any of the following three criteria is met: Increase in SCr by 50% in 7 days, increase in SCr > 0.3 mg/dL in 48 h, or oliguria [Table 1].

The wide range of incidence of cardiac surgery-associated AKI (CSA-AKI) depends on its definition. The severity of CSA-AKI ranges from asymptomatic to requirement for RRT that has a dramatic impact on operative mortality and ICU and hospital length of stay. Approximately 20% of patients will develop AKI, with a 1% requirement for RRT and a 90-day mortality rate of 8%.

RIFLE has been done to identify progressively worsening degrees of renal dysfunction. The function of the kidneys is both elimination of nitrogenous waste products and production of urine; either SCr/GFR criteria or urine output criteria can be used in these models. The incidence of AKI with both AKIN and RIFLE criteria was mostly equal. KDIGO criteria demonstrate greater sensitivity to detect AKI and predict inhospital mortality.[11] In time, the KDIGO criteria will supplant the RIFLE and AKIN criteria but still do not come close to identify AKI at the time of renal insult and to provide no information on the nature of the injury, for example, prerenal syndrome versus established injury, ischemic versus nephrotoxic insults, and oliguric versus nonoliguric renal failure.

ETIOLOGY, PATHOPHYSIOLOGY, RISK FACTORS

Etiology

The complex effects of cardiopulmonary bypass (CPB) often induce some degrees of AKI. Mechanisms include renal hypoperfusion from low-flow, low-pressure nonpulsatile perfusion with hemodilution and hypothermia, as well as inflammatory response that may maintain afferent arteriolar constriction. In the early postoperative period, the most common cause of a further renal result is a low cardiac output state.[12,13] When a low cardiac output state or hypotension persists, the kidney compensatory reserves gradually become exhausted, filtration reserve is exceeded, and endogenous and/or exogenous vasopressors increase afferent arteriolar resistance, resulting in a fall GFR. At this point of prerenal azotemia, oliguria may occur,

Table 1: Comparison of RIFLE (Risk, Injury, Failure, Loss End-Stage Kidney Disease), AKIN (Acute Kidney Injury Network), and KDIGO (Kidney Disease: Improving Global Outcome). Classifications of AKI

	RIFLE	Stages	AKIN	Stages	KDIGO	Urine output
Definition	SCr >1.5 baseline over 7 days		SCr >1.5 baseline over 48 h or↑SCr of 0.3 mg/dl over 48 h		SCr >1.5 baseline over 7 days or↑SCr of 0.3 mg/dl over 48 h	Urine output
Class risk	↑SCr×1.5 or↓GFR >25%	Stage 1	SCr >1.5 baseline or>0.3 mg/dl increase	Stage 1	SCr >1.5 baseline or>0.3 mg/dl increase	<0.5 mL/kg/h×6 h
Injury	↑SCr×2 or↓GFR >50%	Stage 2	SCr >2 baseline	Stage 2	SCr >2 baseline	<0.5 mL/kg/h x 12 h
Failure	↑SCr×3 or↓GFR >75%	Stage 3	SCr >3 baseline or↑SCr to 4.0 mg/dl (with an acute increase of at least 0.5 mg/dl) or↑of RRT	Stage 3	SCr >3 baseline or↑SCr to 4.0 mg/dl or↑of RRT	<0.5 mL/kg/h×24 h
Loss	Persistent acute renal failure with complete loss of kidney function >4 weeks					
ESKD	RRT required for >3 months					

AKIN: Acute Kidney Injury Network, GFR: Glomerular filtration rate, KDIGO: Kidney Disease: Improving Global Outcome, OR: Odds ratio; RIFLE: Risk, injury, failure, loss end-stage kidney disease, RRT: Renal replacement therapy, SCr: Serum creatinine concentration, EDKD: End-Stage Kidney Disease

but tubular function may still intact. A more prolonged period of ischemia will cause structural tubular injury with cell disruption that may obstruct the tubules with back leakage of fluid into the circulation. There are also oxidant injury and inflammatory phenomena that result in further hypoperfusion and damage to tubular cells.

Pathophysiology

The pathogenesis of AKI after cardiac surgery is not completely understood. It is very unlikely that a single etiologic factor will cause perioperative AKI. It is the consequence of multiple, interactive of preoperative, intraoperative, and postoperative pathways.

Recently, genetic predisposition to AKI has been studied. Genetic polymorphisms of all the proteins involved in the different injurious pathways (oxidative stress, inflammatory response) have been investigated. Apolipoprotein E (APOE) is important to lipoprotein metabolism, tissue repair, and immunomodulation. It possesses three alleles: APOE ε2, ε3, and ε4. According to many polymorphism studies, APOE was associated with AKI and its ε4 allele has been the only genotype protective against AKI compared to other forms of allele.[14,15] It reduces postoperative increase in SCr and a lower peak SCr after cardiac surgery.[16]

The greatest influence on renal outcome is the complexity and emergent nature of the cardiac surgical procedure.[17] Two aspects of CPB are critical for favoring the onset of AKI: inflammatory state and hemodilution. The carrying capacity of oxygen is decreased by hemodilution, which is inevitable during CPB. This plus a nonpulsatile flow puts the kidney at danger of ischemia.[18] Hematocrit levels less than 24% increase the risk of CSA-AKI.[19-22] The kidney medulla is more vulnerable since its oxygen delivery is already low. Prolonged duration of CPB, prolonged aortic cross-clamping, cardiac ischemia-reperfusion injury, and low cardiac output syndrome are some factors that influence renal blood flow and trigger renal ischemia besides of the tubular insults associated with the inflammatory response, tubular oxidative stress, exogenous and endogenous toxins, metabolic abnormalities, and neurohormonal activation.[1]

Khan *et al*. examined the role of blood transfusion in causing CSA-AKI on 1210 adults. They concluded that the risk of AKI was highest in patients receiving more than two-unit red blood cells (RBCs). However, they also acknowledged that the study was limited by being observational; there was no set transfusion trigger; the age of RBCs was variable; and a direct causal relationship between RBC transfusion and AKI could not be confirmed.[23]

Risk factors

Patients may be more susceptible to CSA-AKI by their sex, age, preexisting cardiac dysfunction, preexisting chronic kidney disease (CKD), previous cardiac surgery, or comorbidity such as chronic obstructive pulmonary disease or diabetes mellitus.[24] This pathological background is often exacerbated by the frequent administration of nonsteroidal anti-inflammatory drugs (NSAIDs), diuretics, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor blockers, which also contribute to impair glomerular hemodynamics.[25] The risk of developing postoperative AKI is very low (<2%) when a patient with normal renal function undergoes an uneventful operation and maintains satisfactory postoperative hemodynamics. The presence of any degree of preoperative renal dysfunction increases the risk of postoperative AKI and mortality.[3-8]

Renal dysfunction is commonly defined as a SCr >1.5 mg/dL or >130 μmol/L. However, the SCr is not an ideal mean of assessing kidney function because it may be normal with a greater than 50% reduction in GFR, which reflects the number of functioning nephrons. A more sensitive estimate of renal function can be obtained using the creatinine clearance, which approximates the GFR.[26,27] A GFR <60 mL/min/1.73 is the best definition of renal dysfunction and is the level below there is an increased risk of worsening.[4,5]

The Cockcroft–Gault formula employs age and weight as well as gender to calculate GFR. The formula is useful due to simplicity and ease of calculation, and it underscores the importance of age in estimating GFR:

$$\text{Cockcroft} - \text{Gault formula CCr} = \frac{(140 - \text{age}) \times \text{wt (kg)} \times (0.85 \text{ if female})}{72 \times \text{SCr (mg/dL)}}$$

The 2005 Modification of Diet in Renal Disease (MDRD) formula is usually considered a more precise measure of abnormal renal function, which estimates GFR using the variables of age, gender, race, and SCr.[28] This formula estimates GFR more precisely in patients with CKD. Nevertheless, MDRD underestimates GFR

in healthy individuals with creatinine clearance more than 60 mL/min. Furthermore, compared to the Cockcroft–Gault equation, MDRD does not adjust for body mass index and thus underestimates GFR in obese and overestimates GFR in underweight people:

$$\text{MDRD GFR} = 186 \times \text{SCr}^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black}).$$

Cockcroft–Gault overestimates and MDRD underestimates GFR in healthy population.[29] Renal insufficiency in cardiac surgery is acute in onset and most probably in patients without any history of CKD. These formulas may, therefore, not be as useful in this group of patients.

The CKD Epidemiology Collaboration (CKD-EPI) equation is a newly developed and validated formula for eGFR that is more accurate than MDRD. It is more accurate at normal or near-normal GFR and provides more accurate risk stratification than the MDRD in patients at high risk for cardiovascular disease, including identification of increased risk at mildly decreased eGFR.

$$\text{CKD-EPI GFR} = 141 \times \min(\text{SCr}/\kappa, 1)^{\alpha} \times \max(\text{SCr}/\kappa, 1)^{-1.209} \times 0.993^{\text{age}} \times 1.018 \text{ (if a woman)}$$

where κ is 0.7 for women and 0.9 for men, α − 0.329 for women and −0.411 for men.

A milder degree of renal dysfunction is associated with adverse renal outcomes and greater mortality.[6-8,29-32] The risk of AKI is increased 4.8-fold for each 1 mg/dL increment in SCr. AKI severe enough to require RRT is infrequent (1–4%), but the operative mortality in these patients ranges from 40% to 80%.[33-36] This emphasizes the crucial importance of taking any step possible to preserve renal function in the perioperative period, especially in patients at increased risk. The presence of any degree of preoperative renal insufficiency should therefore lead to a search for potentially treatable causes that might lower the risk of AKI postoperatively. Identifying and correcting the risk factors before surgery and using prophylactic measures previous, during, and after surgery to optimize renal perfusion and tubular function may ameliorate the complications associated with the development of oliguric renal failure. Perioperative risk factors are shown in Table 2.

Table 2: Perioperative risk factors contributing to acute kidney injury

Preoperative factors
Renal dysfunction
Advanced age
Female gender
NYHA III
Cardiac heart failure
Left main CAD
Diabetes mellitus
COPD
Peripheral vascular disease
Liver disease
Low cardiac output states/hypotension (cardiogenic shock from acute MI, mechanical complications of MI)
Medications that interfere with renal autoregulation (ACE inhibitors, NSAIDs)
Nephrotoxins (contrast-induced ATN, especially in diabetic vasculopathy), medications (aminoglycosides, metformin)
Renal atheroembolism (catheterization, IABP)
Interstitial nephritis (antibiotics, NSAIDs, furosemide)
Glomerulonephritis (endocarditis)
Intraoperative factors
Procedure-related
Type of surgery: Valvular, valvular+coronary, emergency, redo surgery
Valvular and combined surgery compared to CABG increase risk 2 4 times respectively
CBP nonpulsatile, low-flow, low-pressure perfusion
Hypothermic CPB
Deep hypothermic circulatory arrest
Duration CBP>100 120 min
Hemodilution
Hemolysis and hemoglobinuria from prolonged duration of CPB
Embolism
Postoperative factors
Low cardiac output states (decrease contractility, hypovolemia, absent AV synchrony in hypertrophied hearts)
Hypotension
Intense vasoconstriction (low-flow states, α-agents)
Atheroembolism (IABP)
Sepsis
Medications (cephalosporins, aminoglycosides, ACE inhibitors)

ATN: Acute tubular necrosis, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, CPB: Cardiopulmonary bypass, MI: Myocardial infarction, NSAIDs: Nonsteroid anti-inflammatory drugs, IABP: Intra-aortic balloon pump, NYHA: New York Heart Association, AV: Atrioventricular, CABG: Coronary artery bypass grafting

CLASSIFICATION

AKI has been divided into prerenal (reduced renal perfusion), renal (intrinsic renal insult), and postrenal (obstructive uropathy) with regard to etiology. In surgical patients, prerenal etiology, followed by renal etiology, is the most common cause of AKI. As volume changes are common during cardiac surgery, CSA-AKI can be divided into volume responsive and nonvolume

responsive, which usually matches prerenal and renal etiologies. Renal etiology of CSA-AKI is caused by various factors, including ischemia and ischemia-reperfusion injury, inflammation and oxidative stress, exogenous and endogenous toxins, metabolic abnormalities, and neurohormonal activation. They can briefly be divided into hemodynamic, inflammatory, and nephrotoxic factors.[37]

Nonoliguric renal failure matches the volume-responsive AKI, is defined as a rise in creatinine with a urine output >400 mL/day, is the most common form of AKI, and may occur after an uneventful operation in a patient with preexisting renal dysfunction or risk factors for its development and occasionally without preexisting factors. Corresponds to the first stage of the RIFLE, it occurs in 20% of the patients with a 1% requirement of RRT, reflects less renal damage, and is associated with a mortality rate of about 5–10%.[38] Most patients can be managed with fluid administration, hemodynamic support, high-dose diuretics to optimize urine output while awaiting spontaneous recovery renal function.

Oliguric renal failure matches the nonvolume-responsive AKI. The key sign is a rapidly progressive and profound reduction in GFR, which has been noted to continue and even progress after the return of renal perfusion to baseline. It occurs when the urine output is <0.3–0.5 mL/kg/h for 12–24 h, corresponds to the second and third categories of the RIFLE system, and occurs 5–7% of the cases from which a 7% needs RRT. Once this is necessary, the mortality rate approaches 50%.[36]

DIAGNOSIS, RENAL BIOMARKERS

The RIFLE, AKIN, and KDIGO criteria have helped in defining and staging AKI. However, they all have important limitations. They were not designed for the early diagnosis of perioperative AKI given that they are based on changes in SCr occurring 48 h to 7 days after the original insult. Furthermore, SCr is affected by age, sex, ethnicity, muscle mass, diet, drugs, and intravascular volume loading, independently of renal function.[39] Moreover, creatinine will not be higher than the normal range until 50% of the renal function is lost.[40,41] Thus, rescue interventions based on RIFLE, AKIN, or KDIGO criteria may be instituted far too late to ameliorate intraoperative or early perioperative AKI. Urine output criteria are notoriously unreliable in predicting AKI, and there is no effort to differentiate prerenal from intrarenal oliguria or ischemic from nephrotoxic kidney injury.[42]

AKI may occur in the absence of oliguria, and oliguria may be the consequence of extrarenal obstruction. The SCr frequently falls after CBP due to hemodilution and may have a delayed rise despite a marked reduction in GFR. These limitations have spurred the search for biomarkers of early AKI that might timely direct intervention that could alter renal outcomes [Table 3]. Very few centers routinely evaluate renal function other than by SCr levels, and in the vast majority of cases, there is little significance to subtle changes in tubular function as long as the kidneys produce a satisfactory urine output with or without diuretics with minimal change in the SCr. Measurement of biomarkers may be the most sensitive means of early detection of AKI.

Use of CPB is associated with an increase in virtually all kidney-specific proteins that are markers for tubular damage. Some of these, such as neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, kidney injury molecule 1 (KIM-1), and interleukin-18 (IL-18), have been shown to be early biomarkers of AKI that correlate with severity and duration of AKI.[43-46] NGAL, cystatin C, KIM-1, and IL-18 may be noted within 2–6 h of surgery and correlate to the extent and duration of AKI.[47] These are valuable indicators that precede elevation in SCr levels. Although cystatin concentration

Table 3: Biomarkers of AKI Clinically Investigated

Biomarker	Origin in nephron
NGAL	Glomerulus, distal tubule, collecting duct
Cystatin C	Glomerulus, proximal tubule
Interleukin-18	Proximal tubule
KIM-1	Proximal tubule
L-FABP	Proximal tubule
NAG	Proximal tubule, distal tubule
Urine aGST	Proximal tubule
Urine BGST	Distal tubule
Netrin-1	Proximal tubule
Hepcidin	Proximal tubule
Urinary calprotectin	Collecting duct
TIMP-2	Proximal tubule
IGFBP7	Proximal tubule
TLR 3	Proximal tubule
β2-microglobulin	Glomerulus

NGAL: Neutrophil gelatinase-associated lipocalin, KIM-1: Kidney injury molecule-1, IGFBP7: Insulin-like growth factor-binding protein 7, TLR: Toll-like receptor, L-FABP: Liver-type fatty acid-binding protein, αGST: Glutathione-S-trasnferase-α, βGST: Glutathione S-trasnferase-β, NAG: N-acetyl-β-d-glucosaminidase, TIMP-2: tissue inhibitor of metalloproteinase-2

reflects baseline GFR more accurately than SCr, NGAL is rapidly induced in renal tubular cells in respond to ischemic injury and detected easily in blood and urine because of its small molecular size, and although its early appearance is independent of GFR, it is generally predictive of a subsequent decline in GFR.[48]

NGAL, or lipocalin 2, is secreted by injured distal tubule epithelial cells and enters the urine via tubular back leak. Measurement of NGAL consistently predicted the incidence and severity of AKI. However, it is evident from recent studies that the diagnostic performance of NGAL is significantly influenced by baseline renal function.[49,50]

KIM-1 is a tubular factor that could be helpful in distinguishing ischemic AKI from prerenal azotemia and chronic kidney disease.

IL-18, a pro-inflammatory cytokine, is detectable in urine 4–6 h after CPB, peaking at 12 h. NGAL and IL-18 also predicted important outcomes such as length of stay in the ICU and hospital, dialysis, and death.[51,52]

Cystatin C is a low-molecular-weight (MV) protease inhibitor freely filtered by glomeruli and completely reabsorbed by tubules, detects AKI 2 days earlier than creatinine, and has been shown to reliably reflect changes in GFR.

Tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein 7 are two novel urinary cell-cycle biomarkers released by cellular stress in the early phase of tubular cell injury caused by a wide variety of insults (inflammation, ischemia, oxidative stress, drugs, and toxins). Both markers are involved in the process of G1 cell-cycle arrest that prevents cells from dividing in the case of damage to the DNA until such damage can be repaired. They appear as "alarm" proteins for other nearby cells in a paracrine fashion. These two biomarkers performed better in prediction of AKI than NGAL, KIM-1, IL-18, or cystatin C.[53]

Its practicability will depend on the development of an easy-to-use and inexpensive point-of-care kit that could be used in the operating room or ICU. No biomarker by itself is an accurate and reliable predictor for the diagnosis and risk estimation in AKI. Combination of biomarkers as a diagnostic panel would probably allow the determination of the risk and severity, as well as the early diagnosis of AKI.[54,55] The ideal biomarker for AKI is noninvasive, specific, and sensitive for the detection of AKI within 24 h and is detected and measured in a rapid and reproducible way. Moreover, it should stratify risk and identify AKI subtypes.[41,55-58] A single biomarker that can fulfill all these criteria has yet to emerge.[48]

Although the SCr may not rise as soon as tubular injury has occurred, it still is the only reliable tool for the assessment of AKI, changes in SCr do reflect changes in GFR, and they are therefore valuable in making the diagnosis of AKI. A fall in SCr is an indicator of renal recovery from AKI and correlates with long-term outcomes.

PREVENTION

Patients with chronic kidney disease are more susceptible to fluid overload, electrolyte abnormalities, and metabolic acidosis. Patients on chronic dialysis should be dialyzed within the 24 h before and after surgery. Intraoperative hemofiltration should be also performed to reduce the positive fluid balance. The overall mortality rate for patients on chronic dialysis undergoing open-heart surgery is approximately 10–15% but even higher in those with advanced New York Heart Association class and those undergoing urgent or emergent surgery. The blood urea nitrogen and creatinine should be allowed to return toward baseline, if possible, before proceeding with surgery.

It is recommended that medications such as nonsteroidal anti-inflammatory drugs, ACE inhibitors, angiotensin II receptor blockers (ARBs), be withheld the day before surgery to minimize their hypotensive effects during bypass, (59,60) and metformin is also withheld because it can cause lactic acidosis. Off-pump coronary artery bypass grafting may be associated with a lower incidence of CSA-AKI although without a decrease in the requirement for RRT.[61] Pre- and intra-operative measures to reduce risk of AKI are noted in Table 4.

Intraoperative measures should be taken to try to augment renal reserve by improving renal blood flow, enhancing the GFR, and preventing tubular damage in patients with known renal dysfunction or risk factors for its development.[61,62] During CPB: prevent hyperglycemia, use heparin-coated circuits or use a miniaturized circuit, which may be beneficial in reducing the systemic inflammatory response. Leukocyte filters may attenuate glomerular and tubular injury.[63,64] This has been shown to lower the levels of microalbumin and retinol-binding protein indexed to creatinine.

Table 4: Pre - and intra-operative measures to reduce the risk of acute kidney injury

Preoperative measures
Withhold metformin the day of catheterization
Avoidance of nephrotoxic drugs
Hydratation
Maintenance of renal perfusion
Use of sodium bicarbonate infusion
Consider use of N-acetylcysteine
Optimize hemodynamics status
Repeat SCr if preoperative renal dysfunction, especially in diabetics, and defer surgery, if possible, until SCr has returned to baseline
Correct all acid–base and metabolic problems
Intraoperative measures
Perform off-pump if possible
Use antifibrinolytics to minimize bleeding
Prevent hyperglycemia
Pump considerations: Maintain high perfusion pressure (>75-80 mmHg), reduce CPB bypass time, consider use of a leukocyte-reducing filter, use of hemofiltration to remove excess fluid
Renoprotection: nesiritide, fenoldopam, sodium bicarbonate
Optimize postbypass hemodynamics

SCr: Serum creatinine, CPB: Cardiopulmonary bypass

Hemofiltration can be performed to remove free water and solutes. This is beneficial in removing excess fluid from patients with heart failure and may improve pulmonary function. Use antifibrinolytics to minimize the bleeding diathesis that commonly accompanies renal dysfunction. ε-Aminocaproic acid is commonly used and is generally safe although it is associated with some degrees of renal tubular dysfunction without a significant change in creatinine clearance. Tranexamic acid is a good alternative. Aprotinin was withdrawn from the market in late 2007 because of its increased risk of renal failure as well as other adverse outcomes.

Maintain high perfusion pressure. The optimal mean arterial pressure to prevent AKI during CPB is unknown. Almost all studies that examine mean arterial blood pressure during CPB have demonstrated conflicting data. Azau *et al*. demonstrated that increasing mean arterial pressure does not reduce CSA-AKI.[65] Autoregulation of renal flow occurs down to a pressure of about 80 mmHg; however, below that, flow is pressure-dependent. Since AKI is more common below a critical level for oxygen delivery, it avoids extreme hemodilution (<24% hematocrit).

Acute kidney injury drug prevention

Nesiritide (β-type natriuretic peptide) has been demonstrated in several studies to provide a renoprotective benefit when used during surgery, primarily in patients with abnormal renal function, patients with impaired ventricular function, and those undergoing high-risk surgery.[66-69] It dilates the renal afferent arterioles, and to a lesser extent, the efferent arterioles, resulting in an augmented glomerular filtration. It exhibits strong natriuretic and diuretic properties. It also inhibits the renin-angiotensin-aldosterone axis. Preliminary experience with human atrial natriuretic peptide in patients with left ventricular dysfunction undergoing coronary artery bypass grafting has shown a similar protective benefit. During CPB, it is given in a bolus dose of 2 μg/kg over 1 min, followed by an infusion of 0.01–0.03 μg/kg/min.

Fenoldopam is a selective agonist of the dopamine 1 (DA_1) receptor that produces a dose-dependent increase in renal plasma flow with a decrease in renal vascular resistance and maintenance of GFR, increases blood flow to the renal cortex and medulla, and inhibits tubular reabsorption of sodium. Thus, it produces diuresis, natriuresis, and kaliuresis.[70,71] It is an alternative to nesiritide to provide renoprotection during CPB. Fenoldopam should be considered in patients with a SCr >1.4 mg/dL, initiating an infusion of 0.03–0.1 μg/kg/min before CPB and continuing in the ICU for about 12 h.

Inconsistent evidence has been found in therapeutic interventions such as preoperative statins, acetylsalicylic acid, N-acetylcysteine, and sodium bicarbonate.[72-74]

MANAGEMENT OF ACUTE KIDNEY INJURY

Avoidance of AKI by preventive measures remains the mainstay of management in high-risk patients.[24,75] Contrast-induced AKI is probably an exception in that it is preventable and manageable by hydration, N-acetyl cysteine, and bicarbonate.[76]

Identification and categorization of high-risk patients allow optimal decision-making for earlier intervention and better management, along with the identification of the patients who do not respond to conventional treatments. Risk prediction models can also be used as research tools to select high-risk patients for performing studies on AKI.

Early aggressive intervention in patients with oliguria and early evidence of AKI may prevent progressive tubular injury and worsening of renal function. Discontinue all potentially nephrotoxic drugs, avoid any diagnostic

study requiring intravenous (iv) contrast, and optimize hemodynamics (treat hypovolemia, increase preload, control heart rate, and treat arrhythmias, improve contractility with inotropes if a low cardiac output is present, reduce afterload with vasodilators, and eliminate drugs that can cause renal vasoconstriction). Do not be aggressive in the reduction of systemic blood pressure in patients with preexisting hypertension and chronic kidney disease. They usually require a higher blood pressure (130–150 mmHg systolic) to maintain renal perfusion. If inotropic drugs with vasodilator properties are used, a α-agent may be necessary to maintain systemic blood pressure. If the cardiac output remains marginal despite the use of multiple inotropes, consider the placement of an intra-aortic balloon pump. Maintaining stable hemodynamics is probably the most important point in kidney protection after cardiac surgery. However, factors such as systemic vascular resistance and autoregulatory systems are responsible for cardiovascular stability during cardiac surgery and are difficult to control.

If oliguria persists despite optimization of hemodynamics, the next step is selection of a diuretic.[24] Studies have shown that loop diuretics do not have a direct effect on renal functional recovery or the natural history of AKI and in fact may increase operative mortality and delay recovery of renal function.[77,78] However, loop diuretics have uniformly been shown to improve urine output and can often convert oliguric to nonoliguric renal failure if administered early. An improvement in urine output suggests that the extent of renal injury is less severe in patients with "diuretic-responsive" renal failure and may portend an earlier decrease in SCr, contributing to an improvement in short- and long-term survival.

Furosemide is given in incremental doses starting at 10 mg iv. Once acute renal failure is established, a dose of 100 mg is given 20–30 min to minimize ototoxicity. If urine output fails to improve, increase the dose of furosemide up to 500 mg iv (limiting the daily dose to 1 g) or use a continuous infusion. Initiate 10–20 mg/h. Alternatively, bumetanide can be used. Various combinations of medications may be effective in improving diuresis such as adding a thiazide diuretic to the loop diuretic. Thiazides block distal nephron sites and act synergistically with the loop diuretics to increase exposure of the distal tubules to solute. This combination is particularly effective in patients who tend to be diuretic resistant. Combine DA with furosemide may be synergistic because of the renal vasodilatation and improved renal blood flow produced by DA. The combination of mannitol plus furosemide may also be synergistic.

Once oliguric renal failure is established, treatment should be directed toward optimizing hemodynamics while minimizing excessive fluid administration, providing appropriate nutrition, and initiating early RRT to reduce mortality and improve survival. The blood pressure should be maintained at a higher level than usual in hypertensive patients whose kidneys may require higher perfusion pressures.

Fluids should be restricted. In a *post hoc* analysis of 244 surgical patients, conservative hydration strategy resulted in more ventilator-free and ICU-free days without an increase in AKI. This support recent observations that positive fluid balance in the immediate postoperative period is associated with an increased incidence of AKI.[75,79]

Colloids are superior to hypotonic or even isotonic crystalloid solutions in expanding intravascular volume. Regarding synthetic colloids, there are no guidelines for choosing a specific fluid to improve renal function. Hydroxyethyl starch (HES) is a nonprotein colloid volume expander. They have retained in the intravascular space better than 5% albumin in conditions of capillary endothelial leakage. Concerns about use of HES center around their effects on renal function and their potential to cause a coagulopathy. Although the high MV compounds are more likely to cause renal dysfunction than lower MV ones, none appear to be immune from this problem. In a systematic review of the comparative safety of colloids, AKI and a dose-dependent increase in mortality were observed in patients with severe sepsis or septic shock who were receiving HES.[80] Impaired coagulation and clinical bleeding were frequently reported after HES infusion, especially in patients undergoing cardiac surgery. In randomized comparisons of different types of HES, observed effects on coagulation and renal function were similar, whereas albumin displayed a more favorable safety profile than did HES. Even the third-generation HES 130/0.4, despite its low MW, was associated with increased risk of death and a requirement for dialysis.[81]

Monitor electrolytes, and blood glucose, eliminate drugs that impair renal perfusion or nephrotoxic agents (ACE inhibitors, ARBs, aminoglycosides, NSAIDs). Delayed

RRT submits patients to the many hazards such as encephalopathy, aspiration, platelet dysfunction and bleeding, impaired wound healing, and resistance to infection. RRT has obviated many of these concerns by avoiding hemodynamic instability in susceptible patients after cardiac surgery. The timing of initiation of RRT remains controversial. It is clear that derangements of, for example, potassium, acid–base balance, pronounced azotemia, and fluid overload (called the "conventional criteria" for initiating RRT) need correction.[82] However, clinicians have difficulty estimating the likelihood of recovery from evolving AKI and this complicates the decision to start RRT. The decision when to start RRT is not merely academic but may impact on outcomes. There is no clear guidance as to when to start RRT can currently be given. In addition, the terms "early" and "late" RRT are subjective and there is no reference definition.[83]

CONCLUSION

The research published reflects the numerous approaches being taken to address CSA-AKI. The pathogenesis of AKI is multifactorial. Hemodynamic, inflammatory, and nephrotoxic factors are responsible and overlap each other in leading to kidney injury.

Given the complex pathogenesis of CSA-AKI, it is unlikely that its incidence can be significantly reduced by only one intervention. Just as a combination of factors working in concert leads to this clinical syndrome, prevention and treatment of CSA-AKI require a multimodal approach where both the premorbid condition of the patient and the particular effects of the cardiac surgical procedure itself are taken into account. Timely intervention requires early recognition of potential and actual kidney injury.

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Conflicts of interest

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