

Perioperative Acute Kidney Injury in Cardiac Surgery

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Abstract:

Acute kidney injury (AKI) is a relatively common complication, occurs in up to 30% of all patients in cardiac surgery and requires dialysis in approximately 2% of patients. The development of AKI after cardiac surgery is associated with increased morbidity and mortality. AKI is caused by a variety of factors, including nephrotoxins, hypoxia, mechanical trauma, inflammation, cardiopulmonary bypass and hemodynamic instability and it may be affected by the clinician's choice of fluids

and vasoactive agents as well as the transfusion strategy used. More timely diagnosis would allow for earlier intervention and could improve patient outcomes. Currently, there are no active treatments for AKI. Therefore, In-depth knowledge of the risk factors and pathogenesis for AKI offers some guidance for the prevention and management of AKI.

Keywords: Acute kidney injury; Cardiac surgery, Nephrotoxins

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Introduction:

Acute kidney injury (AKI) is a relatively common complication, occurs in up to 30% of all patients in cardiac surgery¹ and requires dialysis in approximately 2% of patients², associated with a high mortality, a more complicated hospital course and a higher risk for infectious complications.^{1,2} Currently, there is no active treatment for AKI. Therefore, the focus is on prevention and risk factors management, and in-depth knowledge of the risk factors and pathogenesis for AKI offers some guidance for the prevention and management of AKI.

Definition of AKI

AKI is defined as an abrupt (within 48 hours) reduction in kidney function based on an elevation in serum creatinine level, a reduction in urine output, the need for renal replacement therapy (RRT) (dialysis), or a combination of these factors. Therefore, AKI has been defined as an increase in serum creatinine ≥ 0.3 mg/dL (≥ 26.5 μ mol/L) within 48 h; or an increase in serum creatinine to ≥ 1.5 times baseline, a urine volume of < 0.5 mL/kg/h for 6 hours.³

Classification

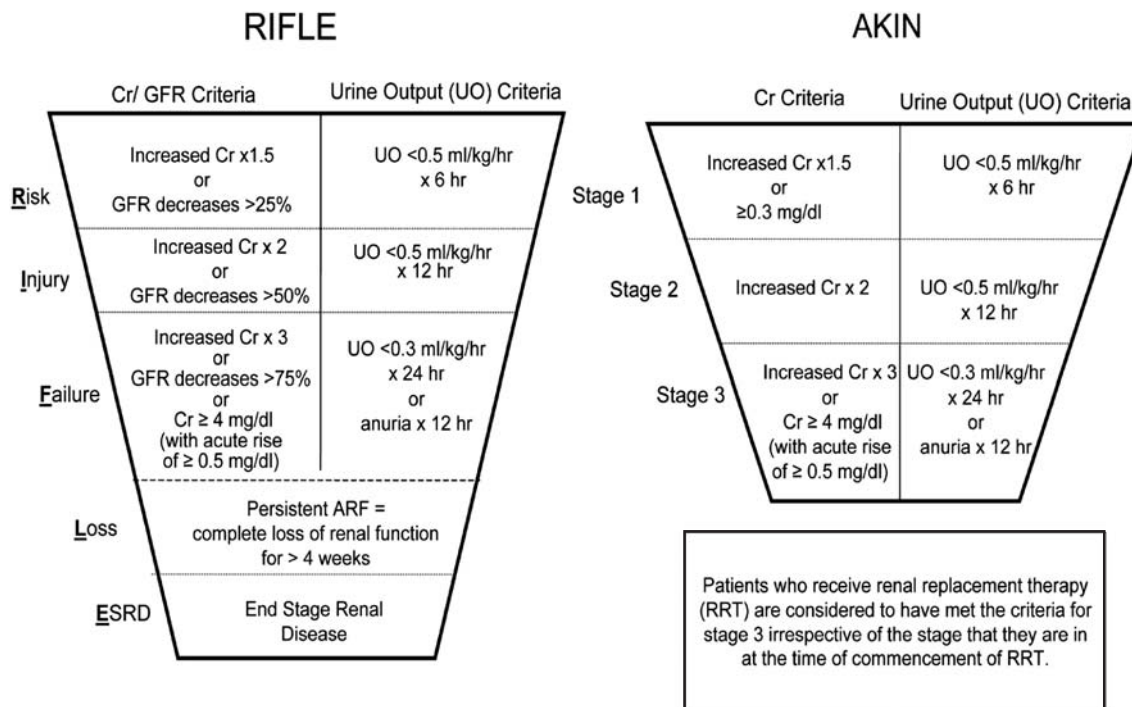
In 2004 the Acute Dialysis Quality Initiative(ADQI) group has published their consensus definition for AKI, the Risk–Injury–Failure–Loss–End stage renal disease (RIFLE) classification. Being a definition, RIFLE uses two criteria: change in blood creatinine or glomerular filtration rate(GFR) from a baseline value and urine flow rates per body weight over a specified time period. In 2007 a modified version of the RIFLE classification has published, also known as the Acute Kidney Injury Network(AKIN) classification (Figure-1). Four modifications are readily recognized: Risk, Injury, and Failure have been replaced with Stages 1, 2 and 3, respectively; an absolute increase in serum creatinine of at least 0.3 mg/dl has been added to Stage 1; patients starting RRT are automatically classified as Stage 3, regardless of their serum creatinine and urine output; and the outcome categories Loss and End stage renal disease have been eliminated.⁴

Importance

On the basis of these standardized definitions of AKI, occurrence rate of RIFLE risk or AKIN stage I and RIFLE injury or AKIN stage II are approximately 17%–49% and 4%–9% respectively after cardiac surgery. In a modern series, the need for RRT ranges from 2%–6%. Patients who require extracorporeal membrane oxygenation in

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ARF= acute renal failure; Cr= creatinine; GFR= glomerular filtration rate

Fig.-1: RIFLE and AKIN classifications for acute kidney injury.⁴

cardiac surgery are at particularly high risk, with 80% incidence of AKI. In patients undergoing pediatric cardiac surgery, the incidences of kidney injury and failure (RIFLE criteria) are 10% and 3%, respectively. Eight percent of pediatric patients undergoing cardiac surgery require dialysis. In adults undergoing cardiac surgery, the development of AKI is associated with prolonged intensive care unit (ICU) and hospital stay and an increased risk of death. AKI in the perioperative period is associated with a higher risk of subsequently developing CKD. RRT is associated with a 2.3-fold increase in the risk of death, and mortality rates range between 25 and 80%.⁵

AKI and Type of Cardiac Surgery

Typical coronary artery bypass graft (CABG) surgery has the lowest incidence of AKI (approximately 2.5%) and AKI that requires dialysis (AKI-D) (approximately 1%), followed by valvular surgery with an incidence of AKI of 2.8% and AKI-D of 1.7%. The highest risk group includes combined CABG/valvular surgery with an incidence of AKI of 4.6% and AKI-D of 3.3%.¹

Risk factors for AKI¹

Patient-Related

- Female gender
- Chronic obstructive pulmonary disease

- Diabetes
- Peripheral vascular disease
- Renal insufficiency
- Congestive heart failure
- LV ejection fraction <35%
- Need for emergent surgery
- Cardiogenic shock (requiring intra-aortic balloon pump, IABP)
- Left main coronary artery disease

Procedure-Related

- Cardio-pulmonary bypass
- Combine valve and CABG surgery

Predictive Scoring Systems

Several groups have developed clinical scoring systems that help predicting the risk for AKI in cardiac surgery. The aim is to select patients who are at high risk and then to adopt strategies that would offer renal protection. A score is given on the basis of 13 preoperative factors and ranges from 0 to 17 (Table 1). In the lowest risk group (score 0 to 2), the risk for AKI-D is 0.4%, whereas in the highest risk group (score 9 to 13), the risk rises to 21.5%.¹

Table-I
Cleveland Clinic Foundation Acute Renal Failure Scoring System

Risk Factor	Points
Female gender	1
Congestive heart failure	2
LV ejection fraction <35%	1
Preoperative use of IABP	2
COPD	1
Insulin-requiring diabetes	1
Previous cardiac surgery	1
Emergency surgery	2
Valve surgery only (reference to CABG)	1
CABG + valve surgery (reference to CABG)	2
Other cardiac surgeries	2
Preoperative creatinine 1.2 to <2.1 mg/dl (reference to 1.2)	2
Preoperative creatinine >2.1 mg/dl	5

COPD= chronic obstructive pulmonary disease; CABG= coronary artery bypass graft.

Minimum score = 0; maximum score = 17

Pathogenesis of AKI

Clinically, the pathogenesis of AKI associated with cardiac surgery can be divided into preoperative, intraoperative, and postoperative events (Table 2). The sum of all of these various insults is ultimately reflected in the development of tubular injury that when severe enough is manifested as a rise in serum creatinine often associated with a decreased urine output.¹

Preoperative Events

Recent myocardial infarctions or severe valvular disease have reduced left ventricular function and reduced renal perfusion. The use of diuretics, non-steroidal anti-inflammatory drugs (NSAID), angiotensin- converting enzyme inhibitors (ACEI), or angiotensin receptor blockers (ARB), impair the auto-regulation of renal blood flow. Lack of renal functional reserve as a result of underlying chronic kidney disease, including small- and large-vessel renovascular disease may increase the vulnerability of the kidney. Ischemic or nephrotoxic insults, inflammatory mediators, endotoxin in the preoperative period also serve to prime the kidney for subsequent injury. Nephrotoxic medications include vasoactive (pressor) drugs, antibiotics or intravenous contrast that is given in the immediate preoperative period may also lead to overt or occult tubular injury.¹

Intraoperative Events

The intraoperative period is a critical time when patients are exposed to anesthesia and cardiopulmonary bypass (CPB). These events lead to dramatic hemodynamic effects as well as activation of both innate and adaptive immune responses that can initiate or extend renal injury. CPB induced inflammation has significant deleterious effects on the kidney. Macroscopic and microscopic emboli, both gaseous and particulate, are temporally related to certain intra-operative events such as aortic cannulation and aortic clamp placement and release. Embolic events to the renal circulation may be responsible in part for postoperative changes in GFR.¹

Table-II
Pathophysiologic factors in AKI

Preoperative	Intraoperative	Postoperative
Lack of renal reserve	Decreased renal perfusion	Systemic inflammation
Renovascular disease	Hypotension	Reduced LV function
Prerenal azotemia	Lack of pulsatile flow	Vasoactive agents
Recent diuresis	Vasoactive agents	Hemodynamic instability
NPO status	Anesthetic effects	Nephrotoxins
Impaired LV function	Embolic events	Volume depletion
ACEI/ARB	CPB-induced inflammation	Sepsis
Nephrotoxins	Nephrotoxins	
Intravenous contrast	Free hemoglobin	
Other medications		
Endotoxemia		
Inflammation		

AKI =Acute Kidney Injury; NPO =Nothing by mouth. ACEI/ARB = Angiotensin- converting enzyme inhibitors / Angiotensin receptor blockers

Postoperative Event

The postoperative events that are critical in affecting renal function are similar to traditional causative mechanisms seen in the general intensive care setting. Thus, the use of vasoactive agents, hemodynamic instability, exposure to nephrotoxic medications, volume depletion, and sepsis/SIRS all are critical events that can lead to kidney injury. In the presence of postoperative left ventricular dysfunction, the risk for significant renal injury becomes very high as the vulnerable kidney is subjected to marginal perfusion pressures.¹

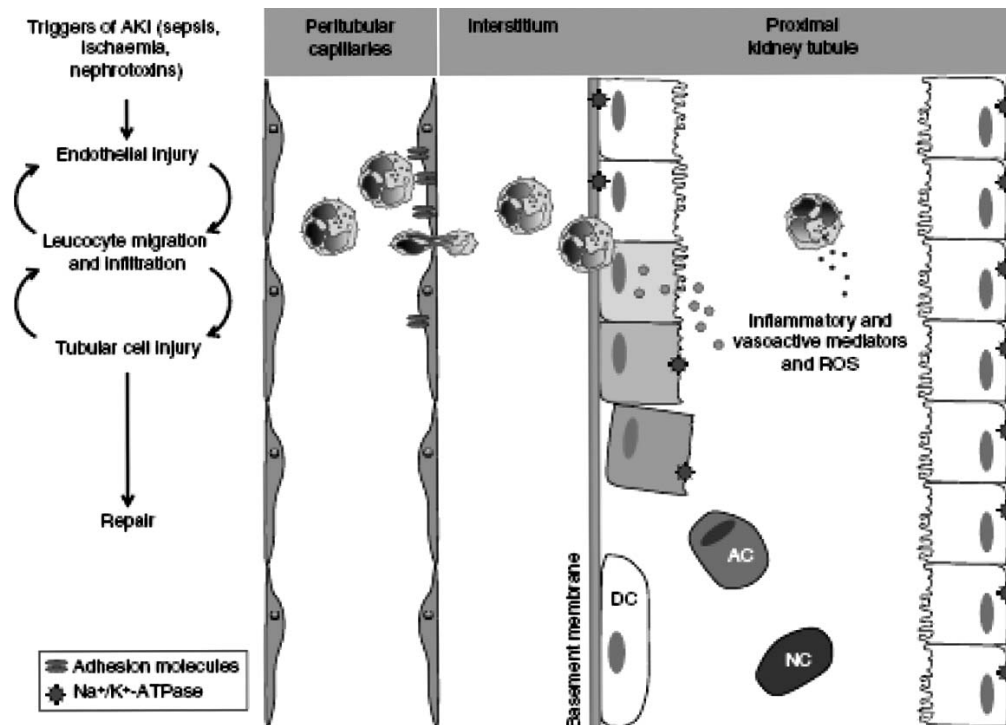
Pathophysiology of AKI

Triggers of AKI (ischaemia, nephrotoxins, and bacterial endotoxins) induce the release of inflammatory mediators (e.g. cytokines and chemokines) from endothelial and tubular cells in the kidney (Figure-2). Neutrophils and other leucocytes migrate to the site of inflammation and marginate along the peritubular capillary wall very early after the insult. Endothelial inflammatory injury is followed by increased vascular permeability which, within 24 h, facilitates migration of neutrophils into the kidney interstitium and tubular lumen. During transmigration,

neutrophils release pro-inflammatory cytokines that further aggravate the tubular injury. Eventually, the tubular response to AKI is characterized by a loss of cytoskeletal integrity leading to desquamation of viable cells and also apoptosis and necrosis. Tubular obstruction from desquamated cells, renal vasoconstriction due to the release of vasoactive mediators, and direct effects on the glomerular filter decrease glomerular filtration rate (GFR) during this process.⁶

Pathology

The prominent findings in human biopsies include detachment of renal tubular epithelial cells from the basement membrane, sloughing of cells into the tubular lumen, effacement and loss of brush border in proximal tubular segments, and the formation of tubular casts derived from sloughed cells, tubular debris, and protein. Interstitial edema is often observed and may develop from leakage of fluid from increased microvascular permeability or backleak of tubular filtrate into the interstitium. Peritubular accumulation of leukocytes in the interstitium has also been observed.⁷



AC =Apoptotic cell; DC =De-differentiating cell; NC =Necrotic cell.

Fig.-2: Pathophysiology of AKI.⁶

Clinical phase of acute kidney injury

Clinically, AKI and the associated decrease in GFR can be divided into initiation, extension, maintenance, and recovery phases. These clinical phases directly relate to cellular events that occur during the injury and recovery process (Figure 3).

Initiation phase

The initiation phase of AKI occurs when renal blood flow (RBF) decreases to a level resulting in severe cellular ATP depletion that in turn leads to acute cell injury and dysfunction. Renal tubular epithelial cell injury is a key feature of the Initiation Phase. Renal ischemia in vivo rapidly induces a number of structural and functional alterations in renal proximal tubular epithelial cells with disruption of the normal framework of filamentous actin (F-actin) in the cell. The extent of these alterations depends upon the severity and duration of ischemic injury.⁷

Extension phase

The extension phase is ushered in by two major events: continued hypoxia following the initial ischemic event and an inflammatory response (Figure 3). Both events are more pronounced in the cortico-medullary junction (CMJ), or outer medullary region of the kidney. During this phase renal vascular endothelial cell damage plays a key role in the continued ischemia of the renal tubular epithelium, as well as, the inflammatory response observed with ischemic AKI. During this phase, cells continue to undergo injury and death with both necrosis and apoptosis predominantly in the outer medulla and the GFR continues to fall.⁷

Maintenance phase

During the clinical phase known as maintenance, cells undergo repair, migration, apoptosis and proliferation in an attempt to re-establish and maintain cellular and tubule integrity. The GFR is stable albeit at a level determined by the severity of the initial event.⁷

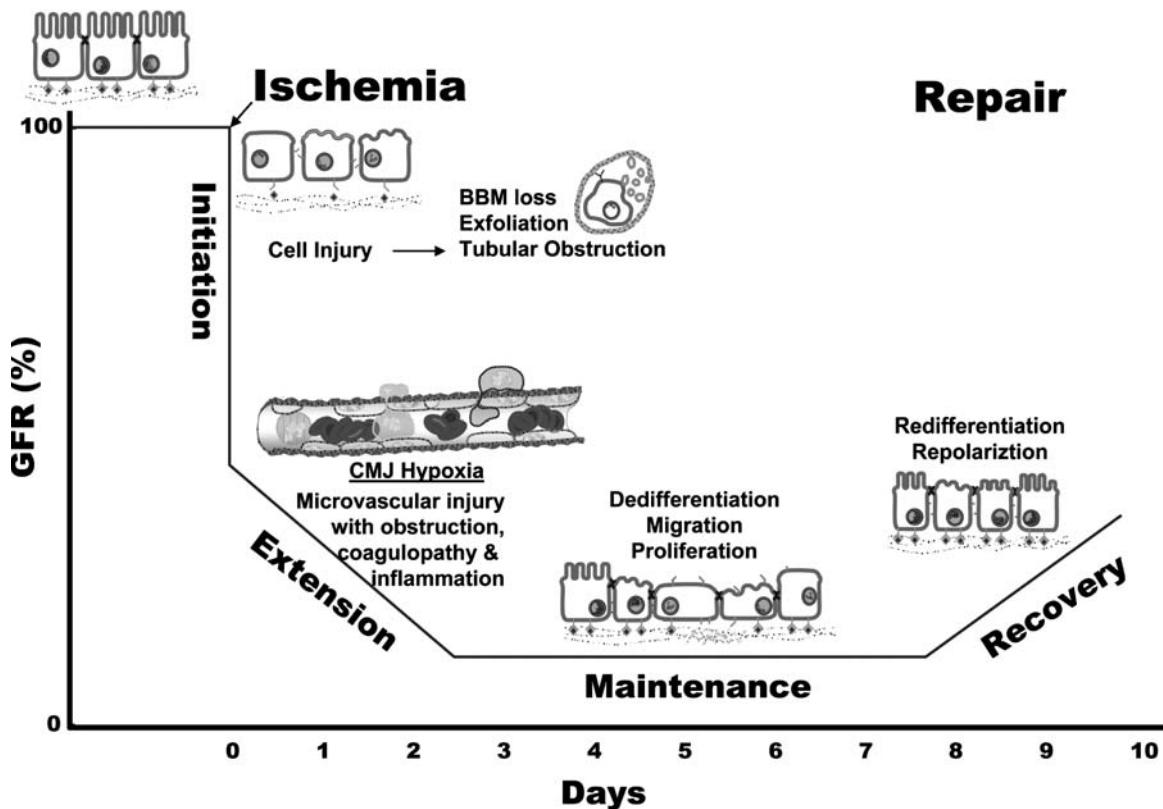


Fig.-3: Relationship between the clinical phases and the cellular phases of ischemic AKI, and the temporal impact on organ function as represented by GFR.⁷

Recovery phase

This cellular repair and reorganization phase results in slowly improving cellular function and sets the stage for improvement in organ function. Blood flow returns toward normal and epithelial cells establish intracellular and intercellular homeostasis. Thus, renal function can be directly related to the cycle of cell injury and recovery and cell response to injury.⁷

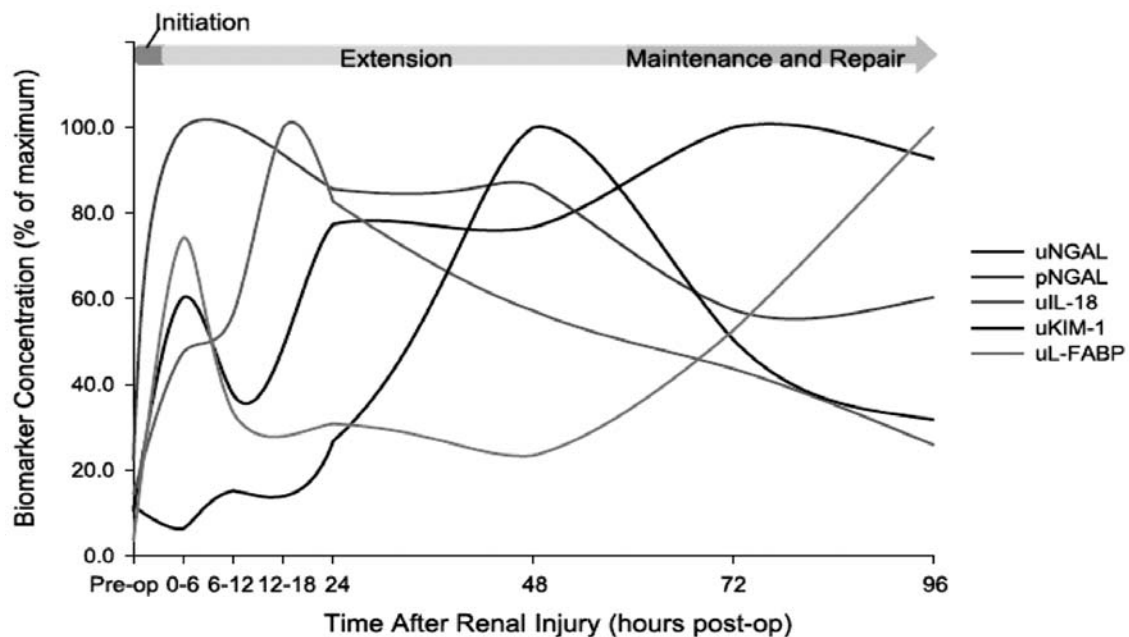
Biomarker-Assisted Diagnosis

Serum creatinine (sCr) concentration does not change until around 50% of kidney function is lost, and varies with muscle mass, age, sex, medications, and hydration status.⁹ The lag time between injury and loss of function, risks missing a therapeutic opportunity, and may explain the high associated mortality. Serum creatinine levels rise 24–72 hours after renal injury. Several plasma and urinary biomarkers develop to diagnose AKI as well as better risk-stratify patients. These include neutrophil gelatinase-associated lipocalin (NGAL), IL-18, cystatin C, kidney injury molecule-1(KIM-1), and others. Preoperative cystatin C performs better than serum creatinine in predicting the risk of AKI postsurgery and preoperative albuminuria as well as brain natriuretic peptide also predictive of postoperative AKI. Postoperatively, urine IL-18 and plasma NGAL peak within 6 hours and these rises are strongly associated with AKI

(AKIN stages II or III). If a kidney biomarker panel is ‘positive’, the patients will have to be monitored intensively, with control over fluid balance, urine output, electrolytes, and functional kidney markers. Equally important will then be to avoid further harm from hypotension, hypovolaemia, contrast agents, and nephrotoxic medications.⁵

Diuretics

Diuretics may reduce the severity of AKI by preventing tubule obstruction and decreasing oxygen consumption. But in a double-blind, randomized, controlled trial, furosemide treatment has found not to be protective as the incidences of AKI are twice that of the dopamine or placebo group. The loop diuretics, which are most frequently used in acute circulatory failure, act by blocking the co-transporter $Na^+-K^+-2Cl^-$ in the ascending limb of the loop of Henle. This blockage enhances the delivery of sodium ions to the macula densa and activates tubuloglomerular feedback; subsequently, the secretion of adenosine increases, and the afferent glomerular arteriole contracts, which is likely to result in more severe ischaemia of the renal medulla. Diuretics intensify the sympathetic system activation and stimulate the renin-angiotensin-aldosterone system and the secretion of vasopressin; they simultaneously impair intrarenal circulation and enhance renal hypoxia.⁹



Pharmacologic interventions for the prevention of kidney injury

Fig.-4: Changes in AKI biomarker concentration over time after renal injury⁸

Dopamine

In low doses (3 mcg/kg per min), dopamine stimulates DA-1 and DA-2 dopamine receptors, increasing renal blood flow and inhibiting proximal tubule sodium reabsorption. Although dopamine has been used extensively, studies have failed to show its efficacy in AKI after cardiac surgery or associated with other conditions. Thus, there is no role for the use of dopamine in the treatment or prevention of AKI.^{1,5}

Fenoldopam

Fenoldopam is a selective DA-1 agonist that has been used in the prevention of AKI with variable results. Small randomized or uncontrolled studies that used fenoldopam demonstrated a reduction of renal dysfunction in patients who underwent cardiac surgery. A potential complication is the associated systemic hypotension that occurs after administration of fenoldopam.^{1,9}

Theophylline

Theophylline, a nonselective adenosine antagonist, is thought to block vasoconstriction induced by A1-adenosine receptors.¹

Atrial natriuretic peptide (ANP)

ANP increases natriuresis by increasing GFR as well as by inhibiting sodium reabsorption by the medullary collecting duct. In patients who have received recombinant human ANP (rhANP), there are a significant reduction in the incidence of dialysis at day 21 after the start of treatment.¹

Mannitol

Mannitol has a variety of effects, including the production of an osmotic diuresis with a reduction of tubular obstruction, as well as the capability of scavenging free radicals. It is often added to the prime solution during CPB to maintain urine output during the procedure, minimize tissue edema, and serve as a free radical scavenger.¹ An early study in children who have undergone cardiac surgery have demonstrated that prophylactic administration of mannitol (0.5 g/kg body wt) are beneficial in the prevention of AKI.

Pentoxifylline

Pentoxifylline, a phosphodiesterase inhibitor, blocks the activation of neutrophils by TNF and IL-1 released by inflammatory cells. Pentoxifylline has been demonstrated to reduce cardiac dysfunction and TNF release in ischemia-reperfusion models.¹

Dexamethasone

Inflammation is well documented to occur during CPB and has a prominent role in the pathogenesis of AKI and CPB. It thus is an attractive therapeutic target. But Dexamethasone has failed to protect against renal dysfunction after cardiac surgery.¹

Clonidine

The sympathetic nervous system is activated during and after cardiac surgery and may lead to impairment of renal function through a hemodynamic mechanism. Clonidine (an α -2 agonist) has been used to attenuate these effects, with improvement in hemodynamic stability and has prevented the deterioration of renal function in this small trial.¹

Diltiazem

Diltiazem has been used in clinical trials to prevent AKI after cardiothoracic surgery. Diltiazem has been shown to inhibit some of the inflammatory effects of CPB and is often used to prevent vasospasm of radial grafts. But its effectiveness in the prevention of renal dysfunction was inconsistent.¹

General Measures to Prevent AKI after Cardiac Surgery

Preoperative

1. Identification of high-risk patients, who undergo cardiac surgery, Identifying patients who are at high risk for AKI is critically important.
2. Optimization of renal perfusion and avoidance of nephrotoxins

Treatment of volume depletion and congestive heart failure before cardiac surgery will increase cardiac output and renal perfusion. Perioperative hydration and the use of hemodynamic monitoring and inotropic agents to optimize cardiac output may be necessary. Medications such as NSAID and other nephrotoxic agents should be discontinued.¹

3. Delay surgery 24–48 h after contrast administration.
4. Optimize glucose control in patients with diabetes (target HbA1c < 7%)
5. Remote ischemic preconditioning (RIPC)

Remote ischemic preconditioning (RIPC) describes the technique of applying mild non lethal ischemia (such as through limb compression with a BP cuff) followed by reperfusion with the goal of protecting other organs from a subsequent episode of ischemia-reperfusion. Although the mechanism of distant organ protection is not known,

it is postulated that humoral, neurogenic, and modulation of inflammatory mediators are involved. A recent meta-analysis of clinical trials of RIPC in patients undergoing cardiac and vascular interventions (11 trials and 1216 patients) showed that RIPC decreased the risk of AKI with marginal significance (OR, 0.70; P=0.06)^{1,5}

Intraoperative

1. Minimize cardiopulmonary bypass and cross clamp times.

There is an association between the use of cardiopulmonary bypass and the development of AKI, with combined surgical procedures (valve replacement and coronary artery bypass) and prolonged cardiopulmonary bypass times increasing the incidence of AKI in adults and children.⁹

2. Base red blood cell transfusions on physiologic data (e.g., SvO₂ and lactate) and not on arbitrary thresholds.

Perioperative blood transfusion has been shown to be associated with organ dysfunction and worse outcomes. Clinical decisions regarding transfusion risk should be on the basis of a complex assessment of oxygen supply and demand matching (including but not limited to measures of cardiac output, venous oxygen saturation, and lactate).^{5,9}

3. Intravenous Fluid Selection

Multiple large RCTs have showed worse renal outcomes in patients who have received HES and the lack of any benefit for the use of any colloid. So it is advised against the use of HES in patients undergoing cardiac surgery and recommend crystalloid solutions.

4. Favor vasopressin over α -agonists to combat vasodilation.

It is reasonable to use either norepinephrine or vasopressin for hemodynamic support in the patient postcardiac surgery. Avoid strict glucose control Patients maintained with moderate parameters (126–179 mg/dl; mean=152 mg/dl) experienced less morbidity and mortality than those maintained by strict (<127 mg/dl) or liberal (>179 mg/dl) criteria.^{1,5,9}

Postoperative

1. Target moderate glucose control

2. Hemodynamic management guided by goal-directed therapy principles.

Goal-directed therapy (GDT) protocols shift the perioperative physician's focus away from traditional hemodynamic end points (e.g., mean arterial pressure

and central venous pressure), the latter of which is not at all predictive of the hemodynamic response to volume loading and has been associated with impaired renal function in a variety of clinical environments and toward more modern end points: either cardiac output, stroke volume, and fluid responsiveness (the expected increase in cardiac index after a volume challenge) or an index of oxygen supply to demand matching (e.g., SvO₂).^{1,5}

3. Transfuse red blood cells to maintain hemoglobin.7.0–8.0 g/dl.

4. Administer diuretics only for specified medical indications

5. Anti-Inflammatory agents.

N-acetylcysteine has anti-inflammatory effects and block oxidant stress, N-acetylcysteine (N-AC) has been shown to block inflammation and oxidant stress in cardiac surgery patients and thus may hold promise as a simple, nontoxic protective measure. N-AC has been studied most extensively in the prevention of radio contrast induced nephropathy.⁹

6. Preemptive Hemodialysis

In patients who are at highest risk for AKI, prophylactic hemodialysis has been attempted. In a single study, 44 patients with a baseline serum creatinine>2.5 mg/dl have been randomly assigned to either perioperative prophylactic dialysis or dialysis only when postoperative AKI that required the procedure has been indicated (control). In the groups that have received prophylactic dialysis, mortality is 4.8 versus 30.4% in the control group. Furthermore, postoperative AKI that required dialysis have been reduced from 34.8% in the control group to 4.8% in the intervention arm.^{1,5,9}

Of available risk modification strategies, several seem particularly promising—minimizing the use of intravenous contrast agents before cardiac surgery, reducing the use of adrenergic agents by adding vasopressin (which has no renal afferent effects) to patients who require vasoactive support, eliminating the use of colloids, which contain HES, restricting the use of exogenous blood products to patients who have symptomatic anemia or present with a compelling physiologic indication (as opposed to passing an arbitrary threshold), and avoiding the use of diuretics, except for specified medical indications

Conclusion:

The pathogenesis of kidney injury is complex and involves hemodynamic, inflammatory, and other mechanisms that interact at a cellular level. At present,

no pharmacologic interventions have demonstrated conclusively efficacy in the prevention of renal dysfunction after cardiac surgery. Ultimately, a successful therapy will utilize strategies that target these multiple pathways.

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