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REVIEW ARTICLE

Cardiac surgery-associated acute kidney injury

Satyen Parida · Ashok Shankar Badhe

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Abstract Cardiac surgery-associated acute kidney injury (AKI) is a major health problem that is extremely common and has a significant effect on cardiac surgical outcomes. AKI occurs in nearly 30 % of patients undergoing cardiac surgery, with about 1–2 % of these ultimately requiring dialysis. The development of AKI predicts a significant increase in morbidity and mortality independent of other risk factors. The pathogenetic mechanisms associated with cardiac surgery-associated AKI include several biochemical pathways, of which the most important are hemodynamic, inflammatory and nephrotoxic factors. Risk factors for AKI have been identified in several models, and these facilitate physicians to prognosticate and develop a strategy for tackling patients predisposed to developing renal dysfunction. Effective therapy of the condition is still suboptimal, and hence the accent has always been on risk factor modification. Thus, strategies for reducing preoperative anemia, perioperative blood transfusions and surgical re-explorations may be effective in attenuating the incidence and severity of this complication.

Keywords Cardiac surgery · Acute kidney injury · Risk factors

Introduction

Acute kidney injury (AKI), previously referred to as acute renal failure (ARF), has an estimated incidence in relation to cardiac surgery of around 30 % [1–10]. Various definitions of AKI have been presented in the medical literature The AKI-RIFLE definition [11] classified AKI into five classes of Risk, Injury, Failure, Loss and End-stage kidney disease (Table 1). The Acute Kidney Injury Network (AKIN) [12] proposed diagnosing AKI based on abrupt (within 48 h) decreases in kidney function (Table 1), recognizing that smaller changes in serum creatinine than those considered by the AKI-RIFLE classification might be associated with adverse outcomes. Accordingly, the AKIN proposed the following modifications to the AKI-RIFLe criteria: (1) the RIFLE "Risk" category could be classified as stage 1 AKI; (2) the "Injury" and "Failure" categories could be classified as stage 2 and 3, respectively; (3) The "Loss" and "End-stage kidney disease" could be removed from staging as they actually qualified as outcomes; (4) patients receiving renal replacement (RRT) could be classified in stage 3. Further, the AKIN classification uses a 48-h window for assessment of renal function, whereas the RIFLE classification uses a 7-day window.

The incidence of AKI requiring dialysis following cardiac surgery is around 1–2 % [1–10]. Outcomes from cardiac surgery are significantly altered by the occurrence of AKI in the perioperative period with increased mortality and morbidity rates as well as increased infectious sequelae reported [1–10].

In this review of cardiac surgery-associated acute kidney injury, we performed a literature search of Medline from 1966 to March 2010 using the Ovid Interface and of EMBASE from 1980 to March 2010 using the keywords "cardiac surgery," "acute kidney injury," "acute renal failure" and "renal replacement therapy" to identify relevant articles. A total of 133 papers were identified, 76 on Medline, 46 on EMBASE and 11 by hand searching of reference lists.

S. Parida (✉) · A. S. Badhe
Department of Anesthesiology and Critical Care, Jawaharlal Institute of Postgraduate Medical Education & Research (JIPMER), Qr. No. E-44, JIPMER Campus, Dhanvantari Nagar, Pondicherry 605006, India
e-mail: jipmersatyen@gmail.com

Table 1 Comparison of RIFLE and AKIN definitions for acute kidney injury

AKI-RIFLE[a]			AKIN[b]		
Stage	GFR or serum creatinine	Urine output	Stage	Serum creatinine	Urine output
Risk	GFR decrease of >25 % or creatinine increase of ×1.5 (baseline)	<0.5 ml/kg/h for >6 h	1	Increase in serum creatinine of ≥0.3 mg/dl (≥26.4 μmol/l) or increase of 150–200 % (1.5- to 2-fold) from baseline	<0.5 ml/kg/h for >6 h
Injury	GFR decrease of >50 % or creatinine increase of ×2 (baseline)	<0.5 ml/kg/h for > 12 h	2	Increase in serum creatinine of >200–300 % (>2- to 3-fold) from baseline	<0.5 ml/kg/h for >12 h
Failure	GFR decrease of >75 % or creatinine increase of ×3 (baseline) or level of 4 mg/dl with an acute increase of 0.5 mg/dl	<0.5 ml/kg/h for >12 h	3	Increase in serum creatinine of >300 % (>3-fold) from baseline (or serum creatinine of ≥4.0 mg/dl (≥354 μmol/l) with an acute increase of at least 0.5 mg/dl (44 μmol/l)) or RRT	<0.3 ml/kg/h for 24 h or anuria for 12 h
Loss	Persistent AKI = Loss of renal function for >4 weeks				
End-stage kidney disease	End-stage kidney disease for >3 months				

RIFLE Risk, Injury, Failure, Loss, End-stage kidney disease, *AKIN* Acute Kidney Injury Network, *AKI* acute kidney injury, *GFR* glomerular filtration rate, *RRT* renal replacement therapy

[a] Renal assessment window up to 7 days

[b] Renal assessment time window up to 48 h

Incidence

Depending upon the definition of AKI used, its overall incidence in relation to cardiac surgery has been reported to be around 30 %, with about 1–2 % of these patients requiring RRT [13]. This high incidence may be related to changing diagnostic criteria of AKI [14]. Elahi et al. [15] reported that among 1245 patients undergoing coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB), about 5 % of patients with pre-existing renal dysfunction developed AKI following surgery.

Prognosis

Cardiac surgery-associated AKI requiring RRT increases mortality as well as hospital expenses [16–20] as many of these patients require repeated RRT following discharge from the hospital [21]. The long-term mortality rates from AKI sustained during cardiac surgery may be influenced by this subset of survivors who might continue to have persistent chronic kidney disease (CKD) [22]. Mortality rates associated with AKI consequent to cardiac surgery-associated AKI have not diminished in the past decade, despite advancements in medical care [17, 18]. Significantly, even a mild impairment in renal function is associated with increased mortality following cardiac surgery [23–25]. Studies have reported that in patients undergoing CABG surgery, AKI requiring RRT inflates mortality rates up to 50–90 %, compared to <3 % for patients without AKI and that this can also have significant economic consequences [25, 26].

Little is known about long-term survival after complete recovery from AKI. Hobson et al. [27] retrospectively analyzed the 10-year (1992–2002) survival rate of 2973 patients with no CKD history prior to undergoing cardiac surgery but who had AKI perioperatively and graded severity with RIFLE classification. The most interesting finding of this study was that even for patients with apparently 'complete renal recovery' (defined as serum creatinine at hospital discharge of <50 % above baseline), the hazards ratio (HR) for death was 1.28 (95 % confidence interval 1.11–1.48) compared with patients without AKI.

The finding that even mild degrees of kidney dysfunction pose a significant risk of death is of great significance. Whether the mild increase in plasma creatinine may simply be associated with unmeasured elements of comorbidity or whether it may be causally related to mortality is still unknown. If the problem is actually the kidney, then possible mechanisms underlying the excess mortality associated with AKI are likely to be found in the pathophysiological changes resulting from kidney insufficiency and the adverse effects of RRT [28, 29]. Salt and water retention resulting in volume

overload, hyperkalemia and acid–base derangements [30], perhaps leading to decreased blood pressure, cardiac output, hepatic and renal blood flow [31], to insulin resistance and protein breakdown, and even to alterations in innate immunity [32], may all contribute to the excess mortality in this group of patients.

Risk factors

Previous studies have identified important risk factors for AKI after cardiac surgery (Table 2).

Several other risk factors have also been indicated, albeit controversially, as contributing to the increased burden of cardiac surgery-associated AKI, although it must be said that individually they are much less important. Karkouti et al. [33] studied the modifiable factors influencing AKI after cardiac surgery and identified three factors, namely, preoperative anemia, perioperative red blood cell (RBC) transfusions and surgical re-explorations, which if addressed and reduced in incidence, could reduce incidence of AKI. Surgical re-exploration after cardiac surgery has also been associated with an increased risk of AKI [34]. The mechanisms involved might include exacerbation of such factors as hemodynamic instability and surgical trauma. Surgical re-exploration is also associated with anemia and RBC transfusion, as the main reason for re-exploration after cardiac surgery is coagulopathy, leading to excessive blood loss [35].

One of the most controversial risk factors is the comparison of off-pump coronary artery bypass (OPCAB) surgery versus on-pump CABG. Despite several large retrospective trials, conclusive evidence continues to elude clinicians, although the majority of data support a lower risk for AKI in patients undergoing OPCAB, especially in the high-risk group with pre-existing renal dysfunction [36–39]. A single-institution, retrospective cohort study over a 10-year period demonstrated that OPCAB surgeries seemed to confer a mortality benefit in comparison to on-pump CABG surgeries for higher risk patients [40]. The ROOBY trial, a prospective, randomized trial involving 2203 patients, compared clinical outcomes in on-pump CABG against OPCAB surgeries over an 8-year period [41]. In contrast to the results of previous retrospective studies, however, the incidence of patients developing renal failure requiring dialysis in the ROOBY trial was not statistically different between the two groups. The ROOBY trial evoked some criticism, with questions raised regarding the OPCAB experience of the surgeons participating in the trial, the use of residents as primary surgeons and the effect of conversions of surgical procedure on the trials primary outcomes [42]. It was further contended that the patient population of the trial was mainly low-to-moderate risk and that the results shown could not be extrapolated to the high-risk group.

CPB is associated with the release of free hemoglobin and iron due to hemolysis occurring during the procedure [39]. Hemolysis could result from mechanical trauma caused to RBCs due to the use of cardiotomy suction, increased duration of perfusion, occlusive roller pumps, turbulent flow in the oxygenator and blood return through cell savers [39]. Consequently, hemolysis may be associated with increased oxidative stress and consequent renal tubular injury [43].

Some studies have also suggested that hemodilution induced during CPB, with hematocrits of <25 %, may be implicated in renal damage inflicted during the procedure, as measured in terms of alterations in serum creatinine levels [44, 45].

Table 2 Risk factors for acute renal failure in patients undergoing cardiac surgery

Patient-related risk factors	Procedure-related risk factors
Preoperative anemia	Length of CPB
Females	Duration of aortic cross-clamping
COPD	Valvular heart diseases
Diabetes mellitus	Off-pump versus on-pump CABG
Peripheral vascular disease	Nonpulsatile flow
Pre-existing renal insufficiency	Hemolysis
Congestive heart failure	Hemodilution
LVEF of <35 %	
Emergency surgery	
Cardiogenic shock requiring insertion of an IABP	
Left main coronary artery disease	

COPD chronic obstructive pulmonary disease, *LVEF* left ventricular ejection fraction, *IABP* intra-aortic balloon pulsation, *CPB* cardiopulmonary bypass, *CABG* coronary artery bypass grafting

Predictive scoring systems

The first preoperative renal risk stratification model was developed by Chertow et al. [16]. More recently, four predictive risk models for RRT after cardiac surgery have been developed to improve upon the limitations of the previous model [46–49]. The Cleveland Clinic Foundation introduced a scoring system developed by Thakar et al. [46] that is based upon the analysis of a cohort of 33,217 patients. These authors assigned a score (range 0–17) based on 13 preoperative factors (Table 3) in which patients with the lowest scores (0–2) had a 0.4 % risk of developing AKI requiring dialysis, while those with the highest scores

Table 3 Cleveland Clinic Foundation acute renal failure scoring system

Risk factors	Points
Female gender	1
Congestive heart failure	1
LVEF of <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
Coronary artery bypass grafting + valve (reference to CABG)	2
Other cardiac surgeries	2
Preoperative creatinine level of 1.2 to <2.1 mg/dl (reference: 1.2 mg/dl)	2
Preoperative creatinine level of ≥2.1 mg/dl	5

Minimum score, 0; maximum score, 17

(9–13) had a risk of 21.5 % of developing the same. Mehta et al. [47] used a large study cohort from the Society of Thoracic Surgeons National Cardiac Surgery database, consisting of almost 450 000 patients who underwent CABG alone, mitral or aortic valve surgery alone or the combination of CABG and aortic or mitral valve surgery between July 2002 and December 2004, to derive a predictive model for postoperative RRT, including a bedside tool to calculate the additive risk score. Wijeysundera et al. [48], created a Simplified Renal Index (SRI) in which only eight factors are used to predict postoperative RRT (Table 4). In a validation of three of these predictive scoring models, the Cleveland Clinic score, the Mehta score and the SRI, it was inferred that the Cleveland scoring system offers the best discriminative value to predict postoperative RRT and covers most patients undergoing cardiac surgery [49]. This validation study also concluded that the Cleveland Clinic score could be used to predict the composite end-point of severe AKI *without* RRT, as defined by I-RIFLE and AKIN stage 2. Yet another multicenter study validating and comparing the same three scores concluded that the Cleveland Clinic Score and the SRI discriminated well between low- and high-risk patients and that the Cleveland Clinic score outperformed the Mehta Score [50]. Finally, Palomba et al. [51] designed the Acute Kidney Injury after Cardiac Surgery (AKICS) score based on a cohort of patients who underwent elective surgery at a Brazilian center, which can apparently predict less severe forms of AKI. The variables that are included in the AKICS score are age of >65 years, pre-operative creatinine level of >1.2 mg/dl, pre-operative capillary glucose level of >140 mg/dl, heart failure, combined valve and CABG surgeries, cardiopulmonary bypass time of >2 h, low cardiac output and central venous pressure (CVP) of >14. Overall, it appears that the Cleveland Clinic score developed by Thakar et al. [46] has the best predictive value for postoperative renal dysfunction following cardiac surgery.

Table 4 Simplified Renal Index scoring scheme for estimating risk of postoperative renal replacement therapy

Variable	Points assigned
Estimated GFR (calculated as per Cockroft–Gault equation) of 31–60 ml/min	1
Estimated GFR (calculated as per Cockroft–Gault equation) of ≤30 ml/min	2
Diabetes mellitus requiring medication	1
LVEF of ≤40 %	1
Previous cardiac surgery	1
Procedures other than isolated coronary artery bypass graft or isolated atrial septal defect repair	1
Nonelective procedure	1
Preoperative intra-aortic balloon pump	1

Low risk, ≤1 point; intermediate risk, 2–3 points; high risk, ≥4 points

Pathogenesis

The cornerstone of AKI both following cardiac [9, 52] and noncardiac surgery [53] is ischemic cellular injury, which leads to tubular epithelial and vascular endothelial injury and activation [54, 55]. The GFR of normal healthy individuals is maintained by autoregulatory mechanisms as long as the mean arterial pressure is in excess of 80 mm Hg [55]. During CPB, the mean arterial pressure often remains at the lower autoregulatory limit or frequently descends below it, especially during periods of hemodynamic instability [56]. Moreover, the majority of patients subjected to cardiac surgery would have multiple associated comorbid conditions, would be under medications that could potentially adversely affect renal autoregulation or would have a proinflammatory state, all of which could contribute to an impairment of renal autoregulation [55]. In such patients with pre-existing impairment of kidney autoregulation, even a mean arterial pressure, within what is commonly understood as the normal range, could be implicated in perioperative deterioration of renal function [55].

A single retrospective analysis of epsilon aminocaproic acid in 1502 patients did not find an increase in AKI [56]. Controversial retrospective studies comparing renal and other consequences of aprotinin, tranexamic acid and epsilon aminocaproic acid in large cardiac surgery

Table 5 Pathophysiological factors in acute renal failure

Preoperative	Intraoperative	Postoperative
Lack of renal reserve	Decreased renal perfusion	Systemic inflammation
Renovascular disease	Hypotension	Reduced LV function
Prerenal azotemia	Lack of pulsatile flow	Low cardiac output
Recent diuresis	Vasoactive agents	Vasoactive agents
Nil per oral status	Anesthesia agents	Hemodynamic instability
Impaired LV function	Atheroembolic events	Nephrotoxins
ACEI/ARB	CPB-induced inflammation	Volume depletion
Nephrotoxins	Ischemia/reperfusion	Sepsis
Intravenous contrasts	Transfusion	IABP
Other medications	Low cardiac output	Transfusion
Endotoxemia	IABP	
Inflammation	Nephrotoxins	
Transfusion	Free hemoglobin	
Low cardiac output		
IABP		

ACEI Angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker

populations did find increased AKI and mortality with aprotinin [57, 58]. However, despite these new data [57, 58], whether the increase in serum creatinine outweighs the decrease in bleeding and transfusion requirements during cardiac surgery is still unknown.

Yet another mechanism by which cardiac surgery could perpetrate ischemia-related kidney damage is by generating a strong systemic inflammatory response [59]. Several pro-inflammatory stimuli form part of routine cardiac surgical procedures, such as operative trauma, contact of blood components with the CPB circuit, ischemia–reperfusion injury and endotoxemia [59]. Embolism, low-output syndrome and exogenous catecholamines can all contribute to renal ischemia/reperfusion during cardiac surgery, leading to phosphate depletion, calcium accumulation, oxygen free radical generation, local leukocyte activation, and NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) activation. These changes cause necrosis and apoptotic cell death through caspase activation. Experimentally, caspase or NF-κB inhibition attenuates ischemia–reperfusion-mediated AKI [60]. Inflammation plays a pivotal role in the initiation of ischemic renal damage [55, 56], and the systemic inflammatory response produced by cardiac surgery is perceived to have a similar effect [59]. The generation of free hemoglobin and iron form CPB-related hemolysis is also believed to be related to ischemic kidney injury [59]. Therefore, variables associated with impaired kidney perfusion, CPB duration and hemodynamic instability have repeatedly been shown to be associated with kidney injury after cardiac surgery [59].

Based on the results of physiological studies conducted by Moran and Myers [61] in ten patients with prolonged, severe AKI after exposure to CPB, the presence of large numbers of granular casts in the urine seems to suggest acute tubular necrosis as the pathological lesion. Clinically, the pathogenesis of AKI associated with CPB can be grossly divided according to the timing of the apparent insult to the kidney as preoperative, intraoperative and postoperative (Table 5).

Preoperative events

Most patients undergoing cardiac surgical procedures under CPB have certain predisposing factors towards renal failure. A large number of these patients have a history of recent myocardial infarction, decompensation of valvular heart diseases and significant ventricular dysfunction, with possible decreased renal perfusion. They might also be patients in cardiogenic shock, requiring hemodynamic support, either pharmacological or mechanical, in the form of an intra-aortic balloon pump (IABP). Renal function could be further compromised by preoperative copious diuresis and the use of nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), which adversely impact renal autoregulation [62]. Events such as preoperative hypotension could also incite renal endothelial damage and adversely affect the release of vasodilator substances such as nitric oxide, resulting in a preponderance of vasoconstrictor stimuli from other substances such as endothelin, catecholamines and angiotensin II, thus furthering tubular ischemia and renal injury [63–65]. Patients could also have underlying CKD with baseline decreased renal reserve, as with pre-existing renovascular disease, which could compound the effects of these numerous insults to the kidney. These hemodynamic perturbations make the kidneys of patients subjected to CPB especially vulnerable to any further ischemic or

nephrotoxic insults [66, 67]. There could also be activation of inflammatory mediators preoperatively that could prime the kidney for subsequent injury. Endotoxin levels have been seen to be higher in some patients in the preoperative period despite the absence of any evidence of infection, and these levels have correlated with postoperative myocardial dysfunction [68–70]. These preoperative elevations of endotoxin levels could either reflect poor cardiac output states with intestinal ischemia, resulting in the translocation of intestinal bacteria into the bloodstream, or indicate the quality of preoperative care, such as subclinical catheter-borne infections [71]. Elevated levels of tumor necrosis factor-alpha (TNF-α) have also been reported in patients with congestive heart failure, possibly suggesting stimulation of the immune system [72, 73]. Nephrotoxic drugs and intravenous contrasts used preoperatively could also result in overt or latent tubular injury, which in association with the factors mentioned above could precipitate AKI in these patients. Hence, this compromised preoperative state sets the stage for intraoperative events to unfold, mainly in the patient undergoing CPB, which can tip the delicate balance for the patient and precipitate AKI.

Intraoperative events

During the intraoperative period, the patient is subjected to anesthesia and cardiopulmonary bypass. Both induce significant alterations to the hemodynamic and immune systems which could initiate or exacerbate renal damage.

Hemodynamic effects

While hemodynamic goals for adult patients on CPB have been defined as perfusion pressures between 50 and 70 mm Hg and flow rates of 1.8–2.4 L/min/m^2, the impact of such goals on renal perfusion and oxygen delivery to the kidneys is far from clear. Moreover, whether revising these goals in certain patients, such as those who are hypertensive, could improve renal outcomes is still unresolved. Other events that accompany CPB and could have a possible impact on postoperative kidney functions include hemodilution, hypothermia, non-pulsatile flow and the choice of priming fluids (i.e. crystalloids vs. colloids). However, apart from hemodilution, which affects the oxygen delivery capacity, other factors, such as changes in body temperature and type of perfusion (pulsatile vs. non-pulsatile flow), have not been demonstrated to have a deleterious effect on renal function. Thus, the hemodynamic effects of CPB have the potential to alter regional blood flow to the kidneys and initiate cellular injury, which could initiate renal damage or exacerbate any pre-existing renal dysfunction, although any conclusive evidence to this effect is hard to come by.

Inflammation

Cardiopulmonary bypass initiates a systemic inflammatory response syndrome (SIRS; Fig. 1) [74, 75]. The contact of blood components with the artificial surface of the bypass circuit, ischemia–reperfusion injury, endotoxemia, operative trauma, nonpulsatile blood flow and preexisting left ventricular dysfunction are all possible contributors to the initiation of SIRS [76–78]. With very severe SIRS, one would encounter a combination of organ damage and increased susceptibility to infection [37]. Animal models of renal ischemia–reperfusion injury demonstrate the pathological role of interstitial inflammation and the elaboration of proinflammatory cytokines and reactive oxygen species in the production of tubular injury [79–81]. An inflammatory response similar to the ones encountered in these experimental models is obviously possible on a much wider scale in patients undergoing CPB. Despite marked improvement in perfusion technology, a CPB system that consistently prevents or at least mitigates the contact activation of blood and blood components has not yet been developed; consequently the CPB system itself remains a very strong proinflammatory stimulus [82, 83].

Other events associated with CPB

Certain other aspects of CPB could also render patients vulnerable to renal dysfunction, including the generation of gaseous and particulate emboli, use of aprotinin and the generation of free iron from hemolysis caused by the CPB circuit, although Tuttle et al. [84] could not demonstrate an association between low iron-binding capacity and the risk of AKI after CPB.

Postoperative events

The postoperative factors associated with kidney damage following cardiac surgery include use of vasoactive agents, hemodynamic instability, exposure to nephrotoxic medications, volume depletion, sepsis/SIRS and postoperative cardiac dysfunction necessitating the use of inotropic or mechanical support.

General measures to prevent AKI after cardiac surgery

Identification of high-risk patients

The identification of patients who are at high risk for the development of postoperative kidney damage following cardiac surgery is the logical first step in preventing this complication. The risk factors and scoring systems used for identifying this group of patients have been discussed in

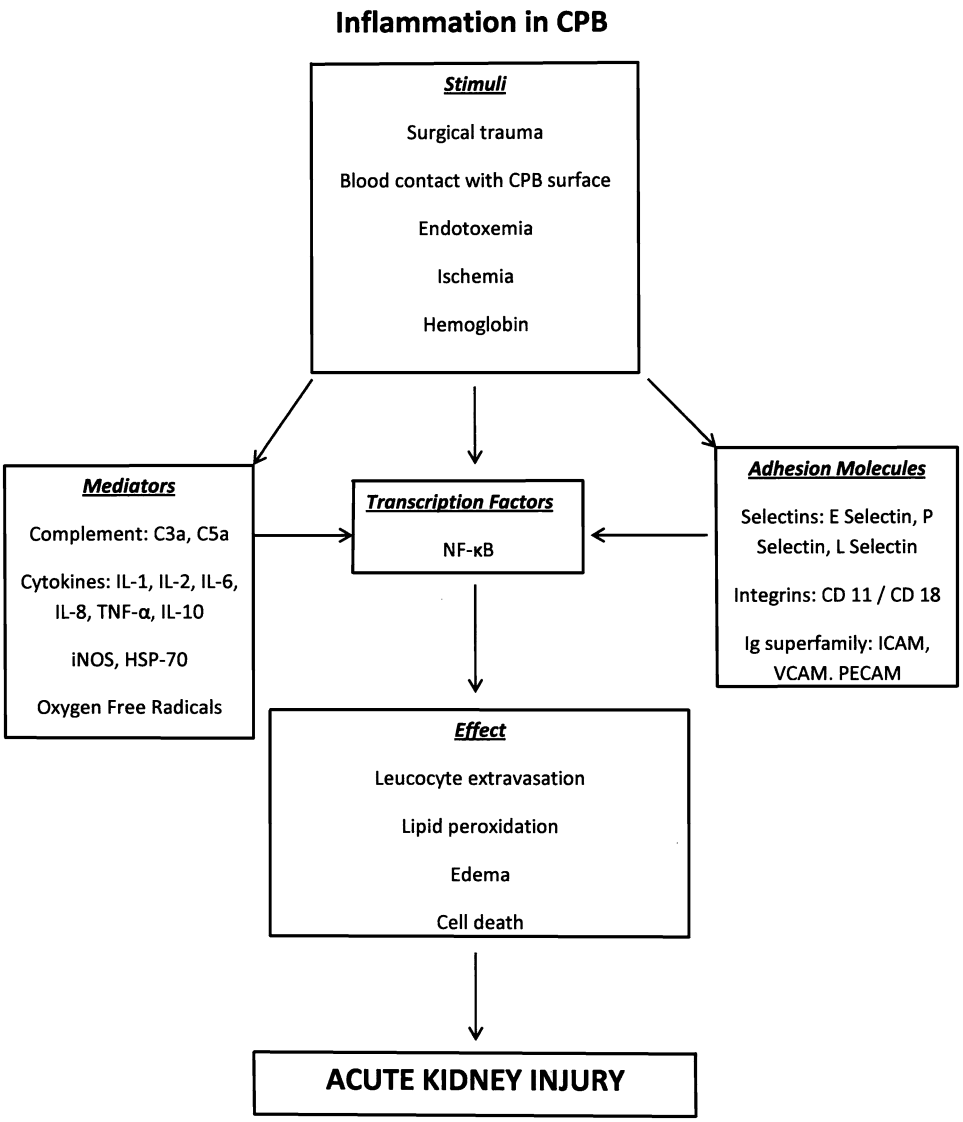

Fig. 1 The inflammatory cascade activated by cardiopulmonary bypass (CPB) surgery and its role in the development of acute kidney injury. *IL* Interleukin, *TNF* tumor necrosis factor, *HSP* heat shock protein, *iNOS* inducible NO synthase, *Ig* immunoglobulin

previous sections of this review. Targeting modifiable risk factors should serve as a reasonable therapeutic aim to minimize the incidence of AKI postsurgery in patients thus identified.

Optimization of renal function and avoidance of nephrotoxins

Factors that lead to a decrease in renal blood flow and cause prerenal azotaemia need to be identified and remedied. For example, correcting volume depletion and optimizing cardiac function in a patient who presents with congestive heart failure would result in an improved cardiac output and consequently improved renal perfusion prior to surgery. Perioperative hydration and rationalization of inotropic agents to optimize cardiac output are important. While it is not clearly known whether the intraoperative optimization of CPB flow, perfusion pressures and oxygen delivery would have a beneficial effect on postoperative renal parameters, it is logical to presume that they would do so. In high-risk patients, NSAIDs and other drugs with nephrotoxic potential are to be avoided. However, whether it would be appropriate to discontinue ACE inhibitors and ARBs before cardiac surgery is not very clear and generates some debate [85–88]. If radiographic agents are required, the newer isosmolar contrast agents may be less toxic [89]. In stable patients, cardiac surgery needs to be deferred if possible until contrast-induced nephropathy has resolved. Similarly, correcting preoperative anemia, limiting perioperative blood transfusions and limiting the incidence of postoperative transfusions could also potentially decrease the burden of AKI associated with cardiac surgery [45]. It has been suggested that preoperative anemia, defined as hemoglobin (Hb) of <12 g/dl, is associated with worse renal outcomes than a preoperative Hb of >12 g/dl, implying that optimizing anemia

preoperatively could potentially improve renal outcomes. In addition, anemic patients, as defined by a preoperative Hb of <12.5 g/dl, presenting for cardiac surgery are more susceptible to transfusion-related AKI than nonanemic patients [90]. Karkouti et al. [91] in yet another unblinded randomized pilot clinical trial suggested that in anemic patients, prophylactic erythrocyte transfusion reduces perioperative anemia and erythrocyte transfusions and may reduce plasma iron levels, which have been linked to deleterious oxidative reactions in the perioperative period. Referring to this study in an editorial remark, Vincent et al. [92], while acknowledging the limitations of this single-center pilot study, concede that the evidence that altered iron metabolism contributes to organ dysfunction after major surgery could have significant bearing on the way clinicians employ blood transfusions perioperatively.

Glycemic control

Severe intra- and early postoperative hyperglycemia, defined as blood glucose levels of ≥200 mg/dl, as well as significant glucose variability, measured as a coefficient of variation during the postoperative period, are stronger predictors of renal function compromise than mere tight glucose control [93]. Maintaining blood glucose concentrations at <180 mg/dl and avoiding large fluctuations in these levels should therefore be an acceptable perioperative goal, rather than tight glycemic control.

Pharmacological interventions to prevent AKI after cardiac surgery

The failure of several pharmacological interventions to prevent AKI after cardiac surgery may be related to a number of factors. Firstly, the pathophysiology of cardiac surgery-associated AKI is a lot more complex than originally believed to be, and hence any therapeutic maneuvers targeting one particular mechanism are likely to fail. Secondly, institution of late therapeutic interventions are unlikely to succeed. Thirdly, most studies have targeted patient population at low risk for developing AKI after cardiac surgery, which may mask the subtle beneficial effects that may be achieved from these pharmacologic interventions. Finally, most clinical trials relevant to this topic have been inadequately powered to detect any subtle beneficial effects of these pharmacologic interventions and make recommendations there from.

Drugs that increase renal blood flow

Low doses of dopamine (3 μg/kg/min) stimulate DA-1 and DA-2 receptors, leading to increased renal perfusion and inhibition of proximal tubule sodium reabsorption. Although dopamine is widely used, studies have failed to demonstrate its efficacy in the prevention or treatment of AKI after either cardiac surgery [94, 95] or in association with any other condition [96]. Hence, there seems to be no apparent role for the use of dopamine in the treatment or prevention of renal dysfunction consequent to cardiac surgery. Fenoldopam [97–99], a selective DA-1 agonist, and theophylline [100], a nonselective adenosine antagonist, have also been used in the prevention of AKI, with variable results.

Drugs that induce natriuresis

Anaritide, a synthetic form of atrial natriuretic peptide (ANP), did not demonstrate a significant beneficial effect when administered to critically ill patients to treat acute tubular necrosis [101], with hypotension being a complicating factor. However, when recombinant human ANP (rhANP) was used to treat AKI after cardiac surgery in patients requiring inotropic support for heart failure [102], there was a significant reduction in the rate of dialysis at day 21 after the start of treatment. In the latter trial, ANP was infused at 50 nm/kg/min, as opposed to 200 ng/kg/min in the former study, and for a more prolonged period, with less consequent hypotension. These changes in the study protocol might account for the beneficial effects of ANP noted in the latter study as opposed to earlier one. Mentzer et al. [103], studied the effects of recombinant human B-type natriuretic peptide (nesiritide) in patients with left ventricular dysfunction undergoing CABG with CPB. These authors demonstrated improved postoperative renal function and possibly enhanced survival in patients receiving nesiritide verus those treated with placebo. These beneficial effects were magnified in the presence of preoperative renal dysfunction and were observed despite the absence of significant hemodynamic changes. A recent meta-analysis [104] systematically reviewed the evidence related to the administration of natriuretic peptides in the setting of cardiovascular surgery associated renal dysfunction. Although most of the studies were inadequately powered, they seemed to suggest significant improvement in clinical outcomes by the administration of natriuretic peptides in patients undergoing cardiovascular surgery. The role of natriuretic peptides need further evaluation in large, adequately powered, prospective, multicenter trials.

It has been proposed that diuretics reduce the severity of AKI by preventing tubule obstruction and decreasing oxygen consumption [105]. However, a double-blind randomized trial comparing furosemide with dopamine and placebo in the context of cardiac surgery found the incidence of AKI to be twofold higher in the furosemide group than in the other two groups [106]. Other studies have also

reported no beneficial effects of diuretics in the management of cardiac surgery-associated renal dysfunction [107, 108]. In the pediatric cardiac surgery setting, mannitol 0.5 mg/kg was found to be beneficial in the prevention of AKI in one study [109]. Fisher et al. [110] reported beneficial effects of mannitol on maintaining urine output at several dosages when added to the CPB prime. However, these findings were not replicated in several other studies, and the role of mannitol in this regard remains controversial [111, 112]. In fact, Carcoana et al. [112] reported the increased excretion of β-2 microglobulin in patients treated with either dopamine or mannitol, indicative of greater tubular damage in these groups. In yet another randomized trial, Sirivella et al. [113] treated postoperative oliguric or anuric renal failure with either intermittent doses of loop diuretics or continuous infusions of mannitol, furosemide and dopamine 2 μg/kg/min. Compared to 90 % of patients in the intermittent diuresis group who eventually required dialysis, the requirement of dialysis in patients randomized to the continuous infusion group was remarkably low at only 6.7 %. Furthermore, early therapy with this cocktail was associated with an earlier restoration of renal function. However, further studies are needed to validate this therapy as being beneficial before a recommendation for wider application can be made.

Other strategies

Drugs having anti-inflammatory effects, including pentoxifylline, dexamethasone, *N*-acetylcysteine (N-AC) and antibodies against complement activation, have all been tried in the prophylaxis and therapy of renal dysfunction following cardiac surgery, but with no clear beneficial effects. In fact, the administration of *N*-acetylcysteine with the goal of protecting the kidney from oxidative stress may not be recommended at all [114]. Clonidine, diltiazem and the use of prophylactic hemodialysis in patients especially predisposed to the development of AKI postoperatively have also been tried, but further studies are mandated prior to framing recommendations for any of these strategies.

Role for prophylactic hemodialysis?

Durmaz et al. [115] attempted prophylactic hemodialysis in patients especially predisposed to the development of postoperative AKI. Their cohort of 44 patients with baseline creatinine values of >2.5 mg/dl were randomized to receive either prophylactic hemodialysis or hemodialysis necessitated by the postoperative development of AKI. The mortality rate of the prophylactic hemodialysis group was 4.8 as compared to 30.4 % in the group in which hemodialysis was offered as therapy for postoperative AKI. The incidence of postoperative AKI requiring dialysis was 34.8 % in the group in which hemodialysis was introduced versus 4.8 % in those receiving prophylactic hemodialysis. However, these results need to be replicated in further trials before prophylactic hemodialysis can be recommended for all patients with pre-existing impairment of renal function.

Recovery from AKI

Another area of interest is the recovery of renal function following AKI [116]. Swaminathan et al. [116] reported that in patients with an identical severity of AKI, those with an early recovery of renal function seemed to have lower mortality risk than those who with a late recovery. Furthermore, the renal recovery variable with the strongest association with 1-year survival was the percentage decrease in creatinine 24 h after its peak value.

Remote ischemic preconditioning and renal protection

Remote ischemic preconditioning (RIPC) is a systemic protective strategy whereby brief limb ischemia confers systemic protection against prolonged ischemia and inflammatory reactions in distant organs. In a study involving patients undergoing abdominal aortic aneurysm repair, RIPC induced by intermittent iliac artery occlusion apparently reduced postoperative renal impairment [117]. However, in patients undergoing complex valvular heart surgery, RIPC did not reduce the degree of renal injury or incidence of acute kidney injury [118]. Similarly, in CABG patients, Rahman et al. [119] concluded that RIPC did not enhance renal protection.

A role for sodium bicarbonate

A pilot randomized controlled trial investigated whether perioperative sodium bicarbonate infusion can attenuate postoperative increases in serum creatinine in cardiac surgical patients [120]. They authors concluded that sodium bicarbonate loading and continuous infusion were associated with a lower incidence of acute renal dysfunction in cardiac surgical patients undergoing cardiopulmonary bypass.

Biomarkers

Although several biomarkers of AKI have either been identified or are currently being investigated, current interest has mainly focused on a few promising biomarkers: neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, interleukin-18 (IL-18), and kidney injury molecule-1 [121]. The NGAL gene is one of the earliest and most upregulated genes following ischemic renal injury

[122], making it a very sensitive and specific biomarker. In a study comparing aprotinin to epsilon aminocaproic acid in patients undergoing cardiac surgery, urinary NGAL was significantly higher at both 0 and 3 h post-CPB in patients receiving aprotinin [123]. Another prospective study compared serum cystatin C and NGAL to serum creatinine in the congenital cardiac surgery setting; both cystatin C and NGAL were found to be very strong independent predictors for AKI as compared to creatinine [124]. However, results on the diagnostic performance of NGAL have been highly variable. While Perry et al. [125] demonstrated that an early increase in post-CPB plasma NGAL is associated with AKI in adult patients undergoing CABG surgery, the sensitivity was as low as 38 %. Owing to the lack of sensitivity and specificity of individual biomarkers, it might be prudent to use a panel of biomarkers to categorize the risk for and outcomes from AKI [126]. Moreover, this wide variability in reported diagnostic performance needs to be addressed before the use of NGAL can be incorporated into clinical practice. Haase et al. [127] suggested that in the absence of diagnostic increases in serum creatinine, NGAL can be used to detect patients with possible subclinical AKI who have an increased risk of adverse outcomes. Hence, such patients could be reasonably classified as having AKI, although they do not fulfil current criteria for AKI.

Genetic risk factors

Genetic risk factors could also be involved in the pathogenesis of AKI, with the possibility of certain gene products being involved in its occurrence. There have been suggestions that sepsis and CPB-related complications could be associated with the polymorphism of genes which participate in the control of inflammatory and vasomotor processes [128–130]. Further studies are required to identify high-risk patients from standardized scores. This might help the nephrologist to take appropriate steps with "at-risk" patients and, consequently, possibly prevent or minimize kidney injury and improve surgical outcomes.

Conclusions

Observations from several studies reinforce the notion that there are many unresolved issues relating to postoperative AKI. The preoperative risk assessment scores will need to be re-validated prospectively using the standardized definitions and should incorporate emerging knowledge of patient characteristics and healthcare elements. However, clinical predictors and biochemical markers identified for the development of AKI can only explain a part of this individual risk, and the roles of early predictive biomarkers, such as urine NGAL, urinary IL-8 and liver fatty acid-binding protein [131, 132], as well as genetic risk factors must not be forgotten.

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