Acute Kidney Injury Post Cardiopulmonary Bypass Surgery

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Abstract: Despite recent advances in the techniques of Cardiopulmonary bypass (CPB), the incidence of and mortality associated with acute kidney injury (AKI) post CPB surgery remain high. Perioperative risk factors for the AKI include advanced age, diabetes mellitus, underlying kidney disease, and poor cardiac function. Attempts should be made to avoid or modify risk factors such as anemia, pre-operative contrast exposure and excessive hemodilution. The benefits of off-pump coronary artery bypass graft (CABG) surgery on AKI remains equivocal. Well controlled randomized studies are needed to further clarify the role of various pharmacologic agents such as atrial natriuretic peptides and Fenoldopam on the prevention of AKI post CABG. Continuous renal replacement therapy is preferable to intermittent hemodialysis in patients needing dialysis.

Keywords: Kidney Injury, Cardiopulmonary Bypass, Coronary Artery Bypass Graft Surgery

1. INTRODUCTION

Acute kidney injury (AKI) remains a serious complication of cardiac surgery with associated increased morbidity and mortality [1-2]. The incidence of AKI post cardio-pulmonary by pass (CPB) surgery ranges from 1-40%, depending on the definition of AKI. Hospital mortality associated with AKI post CPB could range from 50-67% [2-3].

In a meta-analysis, the global pooled incidence of AKI after cardiac surgery was 23% with an associated short and long term mortality of 10.7% and 30% respectively [4]. The variable and inconsistent definition of AKI by investigators likely contributed to the wide range in the published incidence of AKI. The use of widely accepted definition of AKI has facilitated better analysis and comparison of studies. The Acute Dialysis Quality Initiative Group (ADQI) developed a consensus definition for AKI now termed “Risk-Injury-Failure-Loss-End Stage kidney disease (RIFLE) criteria [5]. A modification of the RIFLE was proposed in 2007 by the Acute Kidney Injury Network now known as AKIN classification [6]. Recently, the Kidney Disease Improving Global Outcomes (KDIGO) has proposed a modification that combines the difference between RIFLE and AKIN [7](Table 1).

**Table 1. Classification and Staging for RIFLE, AKIN, and KDIGO Criteria**

<table>
<thead>
<tr>
<th>Class</th>
<th>RIFLE SCr or GFR</th>
<th>Stage</th>
<th>AKIN SCr</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>Increased Scr x 1.5 or GFR decrease &gt; 25% (within 7 days)</td>
<td>1</td>
<td>Increase in Scr ≥ 0.3 mg/dL or ≥ 150% to 200% (1.5-2-fold) from baseline (within 48 hours)</td>
<td>1</td>
</tr>
<tr>
<td>Injury</td>
<td>Increased Scr x 2.0 or GFR decrease &gt; 50%</td>
<td>2</td>
<td>Increase in Scr to more Than 200% to 300% (&gt;2- to 3-fold) from baseline</td>
<td>2</td>
</tr>
<tr>
<td>Failure</td>
<td>Increased Scr x 3.0 or GFR decrease &gt; 75% or Scr ≥ 4.0 mg/dL or acute increase ≥ 0.5 mg/dL</td>
<td>3</td>
<td>Increase in Scr to more than 300% (&gt; 3-fold) from baseline or Scr ≥ 4.0 mg/dL with an acute increase of at least 0.5 mg/dL or initiation or renal replacement therapy</td>
<td>3</td>
</tr>
</tbody>
</table>

Increase in Scr by ≥ 0.3 mg/dL within 48 hours or increase in Scr 1.5 to 1.9 times baseline which is known or presumed to have occurred with the prior 7 days.

Increase in Scr to 3.0 times baseline or increase in Scr to ≥ 4.0 mg/dL or initiation of renal replacement therapy.
Loss Persistent acute renal failure = complete loss of kidney function > 4 weeks

End Stage Kidney Disease End stage of kidney disease (> 3 months)


Biomarkers of renal tubular damage are currently in vogue for the evaluation of AKI. Such markers include: neutrophil gelatinase associated lipocalcin (NGAL), kidney injury marker-1 (KIM-1), urinary Interleukin 18 (IL-18), IGF-binding protein 7 (IGFBP7), tissue inhibitor of metalloproteinase-2 (TIMP-2), liver-type fatty acid-binding protein (L-FABP) and Cystatin C [8]. However, a consensus statement by the ADQI working group has stated that while these markers are useful complement to RIFLE and AKIN definitions of AKI, there is insufficient data to support their use in staging AKI [9].

2. RISK FACTORS FOR AKI

Several risk factors for post cardiac surgery AKI have been well documented [10,11]. Most of these are non-modifiable such as: Age, female gender, underlying chronic kidney disease (CKD), reduced ejection fraction, diabetes, and emergency surgery (table 2). However, some modifiable risk factors not included in the table are: pre-operative anemia with blood transfusion and timing of surgery in relation to radio contrast media exposure. Several small studies have reported that cardiac surgery less than one day after cardiac catheterization is associated with increased risk of AKI post coronary artery bypass graft (CABG) surgery [12, 13]. These studies included patients undergoing both elective and emergency CABG. However, data from the Duke Cardiovascular Disease Data bank revealed that in 2441 patients undergoing CABG surgery after Cardiac Catheterization, the risk of post CABG -AKI was inversely related to the time between cardiac catheterization and CABG [14]. The highest incidence was observed in those operated on in less than one day (24%) and lowest in those operated on after 5 days post cardiac catheterization (15.8%).

Table 2. Risk Factors for Acute Kidney Injury

<table>
<thead>
<tr>
<th>Preoperative</th>
<th>Procedure-related</th>
<th>Postoperative</th>
<th>Nephrotoxic medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Off-pump vs On-pump</td>
<td>Severe sepsis, septic shock</td>
<td>Aminoglycosides, vancomycin, nonsteroidal antiinflammatory drugs</td>
</tr>
<tr>
<td>Female gender</td>
<td>Length of CPB</td>
<td>Hemorrhagic shock</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>Cross-clamp time</td>
<td>Hemolysis</td>
<td></td>
</tr>
<tr>
<td>Pulse pressure &gt;40 mmHg</td>
<td>Non-pulsatile flow</td>
<td>Hemodilution</td>
<td></td>
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<tr>
<td>Chronic kidney disease</td>
<td>CABG + Valve surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>Cardiogenic shock (IABP)</td>
<td></td>
<td></td>
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<tr>
<td>Peripheral vascular disease</td>
<td>Left main coronary disease</td>
<td></td>
<td></td>
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<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>Need for emergency surgery</td>
<td></td>
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<tr>
<td>Congestive heart failure</td>
<td>LV ejection fraction &lt;35%</td>
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<tr>
<td></td>
<td>Previous cardiac surgery</td>
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Table 2. Risk Factors for Acute Kidney Injury
3. ANEMIA AND TRANSFUSION

The renal medulla is in a state of relative hypoxia. Hence the kidneys are vulnerable to hypoxic and oxidative injuries, especially if anemia is present. Many large studies have reported an association between lower hematocrit and increased incidence of AKI post CABG. These studies showed that hematocrit less than 24% during CPB was associated with increased AKI risk. Also, AKI rates increased in direct proportion to the amount of perioperative blood transfusion.

4. STATINS, ASPIRIN AND RENIN-ANGIOTENSIN SYSTEM INHIBITOR (RAS)

Many patients undergoing cardiac surgery are on angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), Statins and or Aspirin therapy. However, it remains unclear if these medication have a protective role in post CABG- AKI. Aspirin is often discontinued 3-10 days before CABG so as to reduce post-operative bleed but continued in emergent CABG patients. An observational study using propensity score and regression analysis suggested that use of aspirin within 5 days of surgery was associated with reduced 30 - day mortality and post-operative renal failure (3.7% vs 7.1%; p <0.001). However, a randomized controlled study “Aspirin and Tranexamic Acid for Coronary Artery Surgery” (ATACAS), found that in patients undergoing CABG the administration of pre-operative aspirin until the day of surgery resulted in neither a lower risk of death, renal failure nor thromboembolic complications.

The beneficial effects of statins in cardiovascular mortality has been well documented but the role of statins in post CABG- AKI remains questionable. In a meta-analysis of over 30,000 cardiac surgery patients it was reported that pre-operative statin use was associated with an absolute risk reduction in mortality, atrial fibrillation and stroke but not myocardial infarction or AKI. However, another study using propensity score, found no difference in the incidence of post CABG- AKI, dialysis or hospital mortality between the statin and the no-statin groups. Thus, the effect of statins and aspirin on AKI post CABG remains unsettled.

5. HEMOLYSIS

Hemolysis is a frequent side effect of CPB and is caused by mechanical shear stress within the extracorporeal system. It may contribute to post CABG- AKI. The AKI is thought to be related to intra tubular hemoglobin precipitation with resultant obstruction versus iron-facilitated oxidant damage to tubulo-epithelial cells and increased intravascular nitric oxide consumption.

6. CARDIOPULMONARY BYPASS (CPB)

Cardiopulmonary bypass is the mainstay of most open heart coronary artery or valvular surgery. It involves the use of an extra corporeal circulation to temporarily replace the function of the heart and lungs during surgery in order to maintain perfusion, oxygenation and carbon dioxide removal. Cardiopulmonary bypass therefore predisposes to AKI through multiple mechanisms: aortic cross clamping with subsequent ischemia –reperfusion injury; lower perfusion pressures; non-pulsatile blood flow, hemodilution; free oxygen radical generation with systemic inflammatory response; and longer duration of CPB. All of these have been associated with increased risk of AKI in a meta-analysis involving over 12,000 patients. It has therefore been hypothesized that preservation of physiologic renal perfusion by avoidance of CPB would decrease the risk of AKI post CABG. The process of performing CABG surgery without the use of CPB is known as “off- pump CABG” (OPCABG). It would therefore seem that avoidance of CPB would minimize renal insult and subsequent post CABG-AKI. The effect of OPCABG on post-operative AKI remains contentious. The Randomized on/off bypass (ROOBY) trial in which 2203 patients were randomized to OPCABG vs. on-pump CABG (ONCABG) failed to show any significant difference in 30- day end points of death, stroke or renal failure requiring dialysis. The OPCABG group also had a worse composite outcome at one year follow up. A large international randomized controlled trial “coronary artery bypass grafting surgery off or On-pump revascularization study (CORONARY) randomized 4752 patients to undergo either ONCABG or OPCABG. Of these, 2932 were enrolled into a kidney function sub study. They observed a significant reduction in 30 day risk of post-operative AKI in the OPCABG than the ONCABG (20.8% VS 17.5%, p =0.01) but there was no difference between the 2 groups in the loss of kidney function at 1 year. On the basis of these studies, the KDIGO-AKI workgroup suggests that OPCABG should not be selected solely for the
purpose of reducing perioperative AKI or the need for renal replacement therapy [17]. The lack of renal benefit in OPCABG is thought to be due to the marked hypotension and increased use of inotropes during the surgery [129].

7. PHARMACOLOGIC PROPHYLAXIS

Multiple pharmacologic agents have been studied over the years for the prevention of AKI. Two agents worthy of mention in this report are Fenoldopam and Natriuretic peptide. Fenoldopam is a short acting dopamine-1 receptor agonist. It increases renal and splanchic blood flow and induces a natriuretic effect [33]. The randomized study in 80 patients by Ranucci et al [32] showed that infusion of Fenoldopam at 0.1µg/kg/ min from start of CPB until 12 hours after surgery resulted in significantly lower rate of AKI (0% vs 10%). A meta-analysis involving 440 patients from 6 studies showed that Fenoldopam significantly reduced the risk of post CABG- AKI (OR 0.41; p=0.003) but a higher rate of hypotensive episodes and or use of vasopressors but no effect on renal replacement therapy [35]. A large multi-center trial would be needed to confirm these results.

The reno-protective effects of human atrial natriuretic peptide (hANP) have been well publicized. A meta-analysis of 13 randomized trials of natriuretic peptides showed better preservation of renal function in patients randomized to perioperative natriuretic peptide infusion [36]. In Japan, ANP is approved for the prevention of AKI and treatment of congestive heart failure [37]. In a study from Japan involving 303 patients with CKD stage 3 (eGFR<60 ml/min per 1.73 m²) were randomized to receive carperitide (synthetic hANP) infusion at 0.02 µg/kg/min vs. saline from start of CPB until 12 hours after oral medication recommenced. The dialysis incident rate through 1 year post operatively was 9% in the placebo group vs. 1.4% in the hANP group, p=0.01. It appears that perioperative infusion of hANP may have a sustained reno-protective effect in CDK patients after CABG. However, the KDIGO AKI working group does not recommend the use of hANP for the prevention of post CABG- AKI [17].

New pharmacologic agents currently under investigation include Levosimendan, a novel calcium sensitizer with inotropic and vasodilatory effects that may offer protective effects in endotoxemic and ischemia-reperfusion injury [36]and ABT-719, a novel α- melanocyte-stimulating hormone analog (αMSH) [37]. A recent meta-analysis of 13 randomized trials involving 1345 patients undergoing cardiac surgery noted that perioperative infusion of Levosimendan reduced the incidence of AKI, RRT, length of intensive care unit stay and death [38]. α-Melanocyte-stimulating hormone is an endogenous hormone that inhibits inflammatory, cytotoxic, and apoptotic pathways, hence prevents renal injury caused by ischemia-reperfusion induced AKI . In addition, α-MSH has direct protective effects on the kidney, which may result from stimulation of the melanocortin receptors in the outer renal medulla [39]. However, a recent phase 2b randomized, double-blind, placebo-controlled multicenter study designed to evaluate the safety and efficacy of ABT-719 in preventing AKI associated with high-risk, OPCABG, ABT-719 treatment did not lower AKI incidence using AKIN criteria, influence the elevations of novel biomarkers, or change 90-day outcomes in patients after cardiac surgery [40]. Further randomized controlled studies will be needed to clearly define the role of these newer agents in the prevention of AKI post CABG.

8. LEUKODEPLETION

Induction of systemic inflammatory response is one of the postulated mechanism of CPB induced AKI. [10, 27]. Hence leukocyte depletion (leukodepletion) using mechanical filtration during CPB has been evaluated for its protective effect on AKI. Most of the published studies are small and appear to show some beneficial effects on reno-protection in patients with mild CKD [39]. A retrospective study of 266 cardiac surgery cases with leukodepletion was compared with a similar group of historical controls but failed to show a difference in renal and other outcomes [41].

9. STEM CELLS

Mesenchymal stem cells (MSC) are known to possess anti-inflammatory and immune regulatory properties that promote cell survival and tissue repair. Infusion of allogeneic MSC in animal models of AKI has been shown to ameliorate AKI [42]. The primary modes of action are thought to be paracrine and endocrine since engraftment of the MSC into target cells were absent and fusion with renal cells were not observed [43]. In a phase 1 randomized trial of
AKI post CABG, preliminary results show that MSC therapy prevented postoperative deterioration in renal function (by ~20%), reduced length of stay (by ~40%), need for readmission (by ~40%), and prevented late deterioration in renal function. [Clinical Trials.gov # NCT 00733876]

10. Remote Ischemic Pre-Conditioning (RIPC)

Remote ischemic preconditioning (RIPC) is a process whereby non-lethal ischemia is briefly induced in a remote organ (typically a limb) so as to provide protection to vital organs in the body against ischemic insults \[^{45}\]. Multiple endogenous molecules including: adenosine, bradykinin, cannabinoids, calcitonin gene peptide and nitric oxide may be humoral mediators of RIPC \[^{45}\]. The beneficial effect of RIPC on the heart has been extensively studied but not on the kidneys. Limited studies on the effect of RIPC on post CABG- AKI produced mixed results. A meta-analysis by Yang et al found no difference in levels of biomarkers of AKI, incidence of RRT and in hospital mortality \[^{46}\]. Similarly a randomized control trial in 86 patients with isolated CABG using three 5 minute cycles of forearm ischemia also failed to show a significant difference in serum or urinary biomarkers of AKI \[^{47}\]. A larger study of 240 patients by Zarbock et al \[^{48}\] observed that fewer patients in the RIPC arm developed post CABG- AKI within 72 hours after surgery (37.5% vs. 52.5% p=0.02). However, a recent meta-analysis of 19 trials with 5100 patients noted RIPC was associated with a significant reduction in AKI post ONCABG but did not impact incidence of RRT, and in hospital mortality \[^{49}\]. Therefore, more randomized studies will be needed to fully evaluate the role of RIPC in post CABG AKI.

11. Renal Replacement Therapy

Renal replacement therapy modality utilized in post CABG- AKI needing dialysis should be dictated by the clinical status of the patient. Both conventional intermittent hemodialysis (IHD), various modalities of continuous renal replacement therapy (CRRT) and hybrid modalities (that combine aspects of IHD and CRRT) are equally effective. Multiple studies that have compared IHD to CRRT could not find any survival superiority or advantages on renal recovery between CRRT and IHD \[^{50,51}\]. Sustained low efficiency dialysis (SLED) is a hybrid modality that has been shown to be equally as effective as CRRT \[^{52}\]. It involves the use of high flux membranes on a low blood flow rate of 100-300ml/min. and a single-pass dialysate flow rates of 100-300ml/min. for about 8-18 hours per day. Older models of dialysis machines are not equipped for such low dialysate flow rates and would need software upgrades that allows for flexible dialysate flow rates and prolonged treatment time. Most current dialysis machines such as Fresenius 2008K, Fresenius 2008T or Gambro 200S ULTRA in the United States are already equipped to allow for hybrid treatments. Further technical discussions on the methodology and function of the Hybrid System is beyond the scope of this review.

High volume peritoneal dialysis (HVPD) is a viable alternative in resource poor regions of the world but requires careful patient selection and strict monitoring of volume status and metabolic balance \[^{53}\]. An effective HVPD requires the use of a “Cycler” which can perform continuous 1-2L exchanges with 30 -60 minutes dwell time for about 18-22 exchanges per day. The absence of a cycler would require the services of a 24 hour dedicated nursing staff. Ultimately, the RRT of choice should be based on several factors including material/ equipment availability, expertise of the nephrologist, vascular access, and hemodynamic stability of the patients.

12. Conclusion

Acute kidney injury incidence post CPB surgery remains high especially in patients with underlying CKD and other risk factors. Mortality and increased resource use are also high. Factors to mitigate the AKI should include: correction of anemia; avoidance of excessive transfusion; and maintenance of adequate perfusion pressures and cardiac output during CPB. Although beneficial effects of RIPC, Fenoldopam, hANP, and Levosimendan on AKI post CABG have been reported, the role of pharmaco-prophylactic agents and RIPC remain largely unresolved. Off-pump CABG may be beneficial in patients with underlying CKD with mild to moderate AKI post CABG. In patients needing dialysis, CRRT is the preferred modality however, dialysis modality should be based on the expertise of the nephrologist, resource availability and hemodynamic status of the patient.

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REFERENCES


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