Acute Kidney Injury Associated with Cardiac Surgery

a report by
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Open heart surgery is one of the greatest medical advances of the 20th century. It is performed worldwide at a rate of nearly 2,000 surgeries per day.[1] Cardiopulmonary bypass (CPB) has allowed surgeons to empty the heart of blood, stop it beating as necessary, open any desired chamber, and safely carry out reparative procedures. The complex physiological derangements associated with CPB can lead to acute end-organ dysfunction in a substantial number of cases. For example, acute renal failure (ARF) or acute kidney injury (AKI), depending on the specific definition, occurs in up to 30% of all patients undergoing cardiac surgery[2–16] (note that these studies represent a comprehensive bibliography assessing the incidence of AKI post-CPB and the incidence of 30% represents the median value found in these studies). Approximately 1% of patients require dialysis.[2–16] The development of AKI is associated with high mortality, a more complicated hospital course, and a higher risk for infectious complications.[16] These data underscore the importance of understanding the pathophysiology of AKI associated with CPB surgery and implementing specific therapies based on this knowledge in well designed clinical trials.

Epidemiological Aspects of Acute Kidney Injury Following Cardiopulmonary Bypass Surgery

In a widely cited study, Conlon et al. described a cohort of 2,843 patients undergoing cardiac bypass surgery (CPB) over a two-year period. AKI (defined as a rise in serum creatinine greater than 1mg/dl above baseline) occurred in 7.9% of patients, and AKI that required dialysis (AKI-D) occurred in 0.7%.[2] Chertow et al. examined the incidence of AKI in a large Veterans Affairs (VA) database of 42,773 patients undergoing CPB, and found an incidence of AKI-D of 1.1%.[16] Most recently, Thakar et al. examined the incidence and outcomes of AKI associated with cardiac surgery between 1993 and 2003.[17] They noted that the incidence of AKI (defined by a ≥50% fall in glomerular filtration rate (GFR) from baseline or need for dialysis) increased over this time period from 5.1 to 6.6%, and the incidence of AKI-D increased from 1.5 to 2.0%. Importantly, despite this increase in incidence, mortality fell from 32 to 23% over this period. Unsurprisingly, given the varying physiological stresses, the incidence of AKI is dependent on the particular type of CPB surgery. Typical coronary artery bypass grafting (CABG) has the lowest incidence of AKI (approximately 2.5%) and AKI-D (approximately 1%), followed by valvular surgery with an incidence of AKI of 2.8% and AKI-D of 1.7%.[18,19] The highest-risk group includes combined CABG and valvular surgery, with an incidence of AKI and AKI-D of 4.6 and 3.3%, respectively.[18,19] Mortality associated with the development of AKI in the setting of CPB is as high as 30% depending on the definition of AKI and the post-operative period studied (hospital discharge or 30-day mortality).[2–16] The highest mortality occurs in patients who require hemodialysis in the intensive care unit, and averages 60–70%.[2,16] However, as mentioned above, recent data suggest that mortality associated with AKI may be improving.[17] In a multivariate analysis adjusting for comorbid factors, Chertow et al. identified the occurrence of AKI-D as an independent determinant of the risk for death with an odds ratio of 7.9.[16] An important and surprising recent finding by Lassnigg et al. has been that even small rises in serum creatinine in the setting of CPB surgery are independently associated with an increase in 30-day mortality.[20] For example, the mortality of patients who developed a 0–0.5mg/dl and >0.5mg/dl rise in serum creatinine was 2.77- and 18.64-fold higher, respectively, than in those patients without a change in serum creatinine.[20] These results are qualitatively similar to those in studies by Thakar et al.,[21] who found that mortality was 5.9% ($p<0.0001$) when GFR declined by 30% or more but the patients did not require dialysis, and 0.4% ($p<0.001$) in those patients with <30% decline in GFR. These studies highlight the important effects of even small derangements in kidney function on the overall outcome of critically ill patients. Furthermore, these effects of AKI also seem to carry over and affect long-term outcomes. Two recent studies demonstrated that those patients with AKI had a higher one-year risk for mortality and that this risk was independent of whether renal function returned to baseline levels.[22,23]

Risk Factors for Acute Kidney Injury and Predictive Scoring Systems

Well validated risk factors associated with the development of AKI post-CPB include female sex, reduced left ventricular function or the presence of congestive heart failure, diabetes mellitus, peripheral vascular disease, pre-operative use of an intra-aortic balloon pump (IABP), chronic obstructive pulmonary disease, the need for emergent surgery, and elevated pre-operative serum creatinine.[3,5–8,15,24–31] This last factor is perhaps the most predictive, with the risk for AKI-D approaching 10–20% in patients with a baseline pre-operative creatinine level of 2–4mg/dl.[24–31] In those patients with a pre-operative creatinine level greater than 4mg/dl, the risk for AKI-D rises to 25–28%.[24–31] Other potential risk factors include those specifically related to the bypass procedure, such as cross-clamp time,[32–34] the duration of CPB (especially if this is >70 minutes),[32–34] pulsatile versus non-pulsatile

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Table 1: Common Risk Factors Associated with Acute Kidney Injury Post-cardiac Surgery

Tier 1—Risk factors with the highest impact
Estimated GFR <30ml/minute
Elevated baseline serum creatinine >2.1mg/dl
Tier 2—Risk factors with intermediate impact
Decompensated congestive heart failure
Left ventricular ejection fraction <35%
Pre-operative use of intra-aortic balloon pump
Emergency surgery
Coronary artery bypass surgery and valvular surgery combined
Repeat cardiac surgery
Serum creatinine 1.2–2.1mg/dl, or estimated GFR 30–60ml/minute
Tier 3—Risk factors associated with lower impact
Diabetes mellitus
Chronic obstructive pulmonary disease
Female gender

GFR = glomerular filtration rate.

Table 2: Pathophysiological Factors in Acute Kidney Injury

Pre-operative	Intra-operative	Post-operative
CKD (stage 3 or higher)	Decreased renal perfusion	Systemic inflammation
Renovascular disease	• hypotension	Reduced LV function
Pre-renal 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/infection
Nephrotoxins	Nephrotoxins	
• IV contrast	• free hemoglobin	
• other medications	• free radicals, oxidative stress	
Endotoxemia	Hemodilution	
Inflammation		
Recent cardiac catheterization		

CKD = chronic kidney disease; LV = left ventricular; NPO = nil per os; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; IV = intravenous; CBP= cardiopulmonary bypass. Source: Rosner MH, Okusa MD, Clin J Am Soc Nephrol, *2006;1:19–32.*

bypass flow,[35,36] normothermic versus hypothermic bypass,[37–39] and on- versus off-pump coronary artery bypass surgery.[40–46]

The question of whether off-pump (OPCAB) is associated with less AKI versus traditional on-pump coronary bypass surgery (CPB) has garnered much attention. OPCAB obviously removes the bypass circuit but can be associated with greater hemodynamic instability secondary to ventricular compression, as the heart is manipulated to access the coronary arteries.[40] A meta-analysis of 37 small, randomized, controlled trials and 22 risk-adjusted observational studies (together encompassing 297,116 patients) demonstrated a trend toward a reduction in AKI in those randomized trials that reported AKI as an outcome measure (odds ratio 0.61, 95% confidence interval [CI] 0.25–1.47).[47] A statistically significant reduction in AKI was seen only in the analysis of the observational studies (odds ratio 0.54, 95% CI 0.39–0.77). Most recently, Hix et al. examined a large, single-center database and analyzed 1,365 patients undergoing OPCAB matched with 1,365 control patients undergoing CPB.[48] They demonstrated a significant two-fold lower risk for AKI in those patients undergoing OPCAB. A prospective, randomized trial examining this issue is now under way (www.clinicaltrials.gov identifier NCT00032630).

Another important risk factor for AKI is hemodilution. During CPB, hemodilution is induced in order to decrease blood viscosity in the hope of improving regional blood flow in the setting of hypoperfusion and hypothermia, as well as limiting the need for blood transfusion.[49,50] The resulting increase in regional blood flow is thought to offset any risk of decreased oxygen-carrying capacity of the blood. However, two recent studies have demonstrated that hemodilution (down to hematocrits lower than 25%) is associated with an increased risk for renal injury as measured by changes in serum creatinine.[51,52] In a retrospective analysis of 1,760 CPB surgery patients, Habib et al. were able to demonstrate that intra-operative hematocrits below 24% were significantly associated with an increased risk for post-operative AKI.[53] These studies highlight the important need for a multicenter, randomized, controlled trial to assess the outcomes associated with various hemodilution protocols. Based on these known risk factors, several groups have developed clinical scoring systems that help to predict the risk for AKI with CPB.[16,29–31,54] *Table 1* lists the common clinical variables that are assessed by these scoring systems, which are very similar. The greatest utility of these scoring systems may be in the design of clinical trials for the prevention of AKI. Given the infrequent nature of AKI (and to minimize the need for large numbers of study subjects), these scoring systems allow investigators to select the highest-risk patients for intervention. These scoring systems are also useful in counseling patients pre-operatively as to their risk for AKI-D, and may allow the early adoption of renal protective strategies.

Pathogenesis of Acute Kidney Injury

The pathological feature of acute tubular necrosis (ATN) is likely the downstream result of multiple events.[55–59] High-risk patients suffer events that lead to pre-renal azotemia, during which interventions to prevent AKI are most likely to be successful. Later, frank AKI ultimately develops if renal perfusion cannot be increased. The development of ATN is heralded by the appearance of sensitive urinary biomarkers such as kidney injury marker-1 (KIM-1), interleukin (IL)-18, or neutrophil gelatinase-associated lipocalin (NGAL) and then later by rises in serum creatinine.[60] The factors involved in the pathogenesis of AKI associated with CPB can be divided into pre-operative, intra-operative, and post-operative events (see *Table 2*). This schema allows clinicians to focus on sentinel events during these critical time periods in an attempt to minimize renal injury.

Pre-operative Events

Patients who require CPB surgery have often suffered initiating events that predispose them to tubular injury. Patients who have had recent myocardial infarctions or severe valvular disease with reduced LV function and reduced renal perfusion often require CBP. This pre-existing pre-renal state may be exacerbated by the use of diuretics, non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme inhibitors (ACEIs), or angiotensin receptor blockers (ARBs), which impair the autoregulation of renal blood flow.[61] Compounding these factors may be a lack of renal functional reserve due to underlying chronic kidney disease, including small- and large-vessel renovascular disease. Furthermore, nephrotoxic medications or intravenous iodinated contrast given in the immediate pre-operative period may also lead to overt or occult tubular injury. In fact, in a recent study cardiac catheterization within five days of surgery was associated with an odds ratio of AKI of 1.82.[62]

Intra-operative Events

The intra-operative period is a vulnerable time due to hemodynamic alterations and activation of the immune system. Supporting the evidence that CPB itself

may be injurious to the kidney are the data presented above, which demonstrate renal protection with OPCAB surgery. Any decrease in renal perfusion during CPB, depending on its magnitude and duration, can lead to significant cellular injury. Generally, CPB flow rates of 1.8–2.2l/minute/m^2 are recommended, along with a mean perfusion pressure of 50–70mmHg.[63–67] Little is known about what the effect of this flow rate and perfusion pressure is on regional renal blood flow and local oxygen delivery rates.[36,66,67] Small studies have suggested that mean arterial pressures on CPB greater than 70mmHg lead to higher intra-operative creatinine clearances but cause no change in post-operative renal function compared with pressures of between 50 and 60mmHg.[68] Thus, it is likely that renal perfusion and autoregulation is also maintained as long as these hemodynamic goals are met. Furthermore, if there is any degree of pre-existing ATN, the autoregulatory capacity of the kidney may be lost and renal blood flow may become linearly dependent on pressure, increasing the vulnerability of tubular cells to ischemia.[69]

Cardiopulmonary bypass provokes a systemic inflammatory response syndrome (SIRS).[70,71] Contact of blood components with the artificial surface of the bypass circuit, ischemia-reperfusion injury, endotoxemia, operative trauma, non-pulsatile blood flow, and pre-existing LV dysfunction are all possible causes of immune activation in this setting.[72–86] These events led to the elaboration of cytotoxic oxygen-derived free radicals, proteases, cytokines, and chemokines.[72–86] The end result of this generalized inflammatory response induced by CPB within the kidney is not known. However, based on animal models of renal ischemia-reperfusion injury, the pathological role of interstitial inflammation, elaboration of pro-inflammatory cytokines, and reactive oxygen species in the production of tubular injury is clear.[56,87–90] Thus, it is likely a safe assumption that CPB-induced inflammation has significant deleterious effects on the kidney through similar mechanisms.

Post-operative Events

Post-operative events, such as the need for vasoactive agents, hemodynamic instability, exposure to nephrotoxic medications, volume depletion, and sepsis/SIRS, are all critical events that can lead to AKI. Perhaps the most critical factor is post-operative cardiac performance and the need for either inotropic or mechanical support of LV function. In the presence of post-operative LV dysfunction, the risk for significant renal injury becomes very high as the vulnerable kidney is subjected to marginal perfusion pressures and extension of ischemic injury can occur. Furthermore, any additional pro-inflammatory insult, such as an infectious complication, may further lead to tubular injury.

Therapeutic Intervention to Prevent Acute Kidney Injury Following Cardiopulmonary Bypass Surgery

In contrast to other complex settings that lead to AKI, CPB affords an opportunity to study protective strategies designed to reduce the incidence of AKI. This is due to the predictable timing of the insult, which allows direct targeting of therapeutics. Furthermore, clinical risk scoring systems allow the detection of those patients at highest risk who are amenable to intervention. Currently, pharmacological interventions have been attempted with inconsistent results, and currently there are no known drugs that have conclusively demonstrated renal protection. This failure is related to a number of factors. First, the pathophysiology of AKI following CPB is complex, and simple approaches to target single pathways are unlikely to succeed. Second, late pharmacological intervention (dictated by the detection of rises in serum creatinine) is likely to meet with failure. Third, patient populations that have been studied are often at low risk for renal dysfunction post-CPB, thus potentially masking small beneficial effects of therapies. Last, most clinical trials enroll a small number of subjects and are inadequately powered to detect small benefits. Therapeutic interventions that have been studied and shown to be ineffective include dopamine,[91–94] theophylline,[95] diuretics,[96–100] mannitol,[101–105] pentoxifylline,[106–109] dexamethasone,[110] and N-acetylcysteine (N-AC).[111–115]

Promising Therapies

Fenoldopam is a selective DA-1 agonist that has been used in the prevention of AKI in small trials with variable results. In patients with CKD undergoing cardiac angiography, fenoldopam failed to reduce renal dysfunction, 30-day mortality, dialysis, or rehospitalization.[116] However, small randomized or uncontrolled studies using fenoldopam have demonstrated a reduction of renal dysfunction in patients undergoing cardiac surgery.[117–119] In one study of 80 patients undergoing cardiac surgery with a baseline creatinine clearance of 50ml/minute, fenoldopam did not reduce the rate of AKI or need for dialysis.[119] Another study of 110 critically ill patients with early renal dysfunction (creatinine ≥1.5 but ≤3.5mg/dl) found that more patients treated with fenoldopam infusions had a decrease in plasma creatinine concentration of ≥10%.[120] However, the mean peak creatinine and urine output did not differ between the two groups.[120] A potential complication is the associated systemic hypotension that occurs following the administration of fenoldopam. The beneficial effect of renal vasodilation in this situation may be offset by systemic hypotension that results in an overall net reduction of blood flow to the kidney. An interesting trial utilizing fenoldopam to increase renal blood flow in combination with MESNA to neutralize free-radical and oxidant injury associated with reperfusion is being planned (www.clinicaltrials.gov identifier NCT00286403).

In a recent study, recombinant human atrial natriuretic peptide (rhANP) was used to treat AKI in post-cardiac surgery patients requiring inotropic support for heart failure.[105] In patients receiving rhANP there was a significant reduction in the incidence of dialysis at day 21 after the start of treatment. In this trial, ANP was infused at a lower rate (50ng/kg/minute compared with 200ng/kg/minute, thus lowering the incidence of hypotension) and for a more prolonged period than in prior studies, which had not demonstrated a benefit. This positive study will need verification in a multicenter, randomized trial before this strategy can be broadly recommended. Recently, the Nesiritide Administered Peri-Anesthesia in Patients Undergoing Cardiac Surgery (NAPA) trial was reported.[122] This was a multicenter, randomized, placebo-controlled trial of nesiritide versus placebo in 303 patients with left ventricular dysfunction (ejection fraction <40%) undergoing cardiac surgery with CPB. The mean duration of study drug infusion was 40 hours. Peri-operative renal function was better in the nesiritide group (lower peak rise in serum creatinine, smaller decrease in estimated GFR, and greater 24-hour urine output). These findings were even more pronounced in the subgroup with baseline renal insufficiency (serum creatinine >1.2mg/dl). Furthermore, length of hospital stay was shorter in the nesiritide group. Several other smaller trials have also shown the protective renal effects of nesiritide in the cardiac surgery population. However, a more definitive trial is needed to confirm these intriguing findings.

Sirivella and colleagues attempted a multifaceted approach to prevent AKI, utilizing agents to increase both renal blood flow and natriuresis.[123] One hundred patients with post-operative oliguric or anuric renal failure were randomized to therapy with either intermittent doses of loop diuretics or a continuous infusion of mannitol, furosemide, and dopamine (2mg/kg/minute).[123] While 90% of patients receiving the intermittent diuretic

required dialysis, only 6.7% of those receiving the continuous mannitol, furosemide, and dopamine infusion required dialysis. Furthermore, early therapy with this 'cocktail' was associated with early restoration of renal function. Further studies are required before this approach can be broadly recommended, but these results are quite striking. In patients at highest risk for AKI, prophylactic hemodialysis has been attempted.[124] In a single study, 44 patients with a baseline serum creatinine higher than 2.5mg/dl were randomized to either peri-operative prophylactic dialysis or dialysis only if post-operative AKI requiring the procedure was indicated (control). In the group receiving prophylactic dialysis mortality was 4.8 versus 30.4% in the control group. Furthermore, post-operative AKI requiring dialysis was reduced from 34.8% in the control group to 4.8% in the intervention arm. These results will have to be repeated in other randomized controlled studies before this invasive approach can be broadly recommended.

Summary

AKI is associated with significant morbidity and mortality. This setting serves as an ideal model system for studying the pathogenesis of AKI and potential therapies. Clearly, the pathogenesis of AKI is complex and involves hemodynamic, inflammatory, and other mechanisms that interact at a cellular level. Currently, there are no pharmacological interventions that have conclusively demonstrated efficacy in the prevention of renal dysfunction following cardiac surgery. However, several recent trials have shown promise with agents that act to affect hemodynamics (ANP, fenoldopam, nesiritide). It is likely that a successful therapy will utilize strategies that target multiple pathways. This integrated strategy would target hemodynamic, inflammatory, and oxidative pathways, and act both at the points of proximal cellular injury and at later downstream events such as tubular regeneration. ■

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