Risk Factors for Acute Kidney Injury after-Cardiac Surgery
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Objective: At the conclusion of this lecture, participants should understand the pathophysologies contributing to, and risk factors for AKI following cardiac surgery.

Acute kidney injury (AKI) commonly complicates cardiac surgery and is highly predictive of outcome including short-term mortality and long-term survival. The kidneys’ inefficient oxygen delivery system and high metabolic rate make them vulnerable to ischemia-reperfusion injury. However, many other factors contribute to the heterogenous disorder termed post-cardiac surgery AKI. In the following document, understanding of AKI, and renoprotection strategies related to cardiac surgery are discussed.

Nearly 500,000 CABG surgeries are performed each year in the US. AKI is a common postoperative complication that appears to be increasing in frequency independent of increasing severity of patient case-mix, perhaps related to more sensitive diagnostic criteria. Risk factors common to heart surgery candidates, including advanced age, diabetes, hypertension, and metabolic syndrome are also predictors of kidney disease, and one out of five patients meet criteria for chronic renal dysfunction preoperatively (e.g., GFR<60ml/min).

Little is known about the effects of cardiopulmonary bypass (CPB) on normal renal physiology. During standard CPB, cardio-renal relationships are approximately preserved; renal blood flow is highly related to pump flow and perfusion pressure, but falls from 25% to 12-13% of total flow, while perfusion pressure stands as the primary predictor of urine output. Notably, no studies have addressed the intactness of renal autoregulatory reflexes during CPB such as myogenic and tubular-glomerular feedback; these normally “protect” the glomeruli from overload by restricting renal blood flow at higher pressures (e.g., >80mmHg).

CPB does appear to adversely affect regulation of microvascular renal perfusion. Notably, during experimental CPB, medullary PO$_2$ drops from normally low levels to unmeasurable. Typical medullary PO$_2$ values are 10-20mmHg; this phenomenon is termed medullary hypoxia and is due in part to marked regional differences in oxygen delivery; cortical blood flow exceeds outer and inner medullary by 3 and 20 fold per gram of tissue, respectively. Oxygen “escape” from parallel vessels (entering to exiting) throughout the kidney, and the high metabolic demand of the outer medulla also contribute. However, the effect CPB on these factors, and paracrine mediators of regional kidney perfusion (e.g., nitric oxide, prostaglandins, rennin-angiotensin system) is not known. Finally, an adenosine receptor-mediated renal ischemic preconditioning reflex has been characterized, but the relevance of this to human CPB is also unknown.

Risk Factors and Mechanisms of Post-Cardiac Surgery AKI
Risk factors for post-cardiac surgery AKI include variables that contribute to or are related to the underlying pathophysiology of AKI. Unlike nephropathies that reflect a single source of insult (e.g., contrast-induced nephropathy), post-cardiac surgery AKI reflects the cumulative consequences of numerous potential perioperative insults that may or may not be relevant to any particular patient (Figure). Common consequences of all AKI are tubular and vascular cell dysfunction, necrosis, and apoptosis. Although interventions remain elusive to influence trigger mechanisms of the reflexive common pathway of AKI, there is better understanding of the direct effects of some specific cardiac surgery renal insults.

In the absence of proven broadly applicable protective interventions, the major thrust of an effective approach to perioperative renal protection involves identifying specific sources of insult for an individual patient that can be changed, and minimizing them.

Thus, while AKI pathophysiology is extensively discussed elsewhere, a brief overview focused towards cardiac surgery is pertinent.
**Inflammation**

Inflammation is an important contributor to cardiac surgery-related AKI. Circulating proinflammatory cytokines are part of the systemic inflammatory response to surgical trauma and CPB. In addition, local release of cytokines related to kidney ischemia/reperfusion is mediated by nuclear factor kappa B (NF-κB) activation. Notably, renal dysfunction also influences the course and magnitude of any inflammatory responses since filtration is a primary clearance mechanism for many cytokines (e.g., interleukin 6, interleukin 1β, tumor necrosis factor-α).

**Ischemia/Reperfusion**

Emboli, low-output syndrome, and exogenous catecholamines can all contribute to renal ischemia/reperfusion during cardiac surgery. These changes cause necrosis, and apoptotic cell death. Apoptosis instigates more local inflammation and injury. Experimentally, caspase or NF-κB inhibition attenuates ischemia-reperfusion mediated AKI.

**Embolism**

Embolic renal infarcts are pizza wedge-shaped, involving adjacent cortex and medulla, and highlight the lack of redundancy and vascular arrangement of the kidney. Fat droplets, particulates, and bubbles are common during cardiac surgery. Intraoperative detection demonstrates numerous emboli, particularly during aortic manipulation (e.g., unclamping). Renal atheroembolism is sometimes a dominant source of cardiac surgical AKI and often observed at autopsy. Atheroma burden and emboli counts predict AKI, and aortic filter devices routinely catch gross atheroemboli after crossclamp removal. Plaque disruption related to intra-aortic counterpulsation also likely contributes to AKI. Anti-atheroembolism strategies have thus been widely adopted, but compelling evidence that this has decreased AKI is not available. One randomized filter device trial found less AKI in a post-hoc analysis of higher risk patients. Embolic complications can occur from other particulates, including septic vegetations, thrombus, platelet fibrin debris, and even normal vessel wall. One third of endocarditis patients suffer significant postoperative AKI. Although reinfusion of blood contaminated by sternal marrow lipid droplets is common and may effect renal blood flow, its importance is unknown. Air bubbles are rarely associated with AKI. Surgical field insufflation of CO₂ reduces intravascular bubbles, but whether this reduces AKI rates has not been assessed.

**Pigments and other Nephrotoxins**

Both myoglobin and hemoglobin avidly bind nitric oxide, causing AKI through direct cytotoxicity, vasoconstrictor effects, and tubular obstruction. Leg ischemia from femoral artery cannulation has been blamed for myoglobinuric AKI. While statins can cause myopathy, these agents have not been associated with increased renal risk in vascular and major non-cardiac surgery patients. The renal safety of antifibrinolytic agents has been questioned. Several studies comparing aprotinin, tranexamic acid, and epsilon aminocaproic acid in large cardiac surgery populations found increased AKI and mortality with aprotinin. Concerns that a bias towards sicker patients receiving aprotinin may have been inadequately addressed by statistical methods complicates interpretation of some of these studies. Nonetheless, the renal risk of aprotinin now figures prominently in discussion of this
agent. Although precedent for tolerating nephrotoxic effects exists in cardiac surgery (e.g., cardiac catheterization and contrast dye), whether and/or in which type of patient any blood-sparing gain of aprotinin justifies added renal risk relative to lysine analogue agents or no therapy remains a topic of significant debate in some circles. However, the withdrawal of aprotinin in most countries has largely settled the issue from a clinical perspective.

Other perioperative nephrotoxins include α adrenergic agonist agents, some antibiotics, non-steroidal anti-inflammatory agents, and cyclosporine. Catecholamine effects influence renal perfusion through α₁-mediated vasoconstriction and dopaminergic and α₂-mediated vasodilation. Experimentally, even short periods of high dose norepinephrine cause long-lasting AKI. Catecholamines in cardiac surgery also predict AKI, but disentangling cause and association for these agents is problematic since they are rarely used in the absence of other major risk factors (e.g., low output state).

Renal Preservation Outcome Studies
Strategies for reducing AKI aimed at risk avoidance, and interventions for prophylaxis referred to as “renoprotection” are collectively reviewed.

Modifiable factors in standard management of cardiac surgery patients
Chronic medications may influence perioperative AKI risk. Long-term diuretic therapy and some studies in patients chronically receiving angiotensin-converting enzyme inhibitors (ACEIs) have been associated with AKI in retrospective studies. Although ACEIs can precipitate AKI with renal artery stenosis, neither isolated continuation of these agents perioperatively or the presence of renal artery stenosis independently predict post-cardiac surgery AKI.

Optimizing volume status with hydration may prevent or attenuate contrast nephropathy and reduce postoperative AKI in some patients. Selection of some hydroxyethyl starch colloids for volume expansion has been shown to increase AKI/dialysis and 90 day mortality risk relative to saline in critically ill, including post-cardiac surgery, patients with sepsis.

Perioperative thoracic epidural local anesthetic blockade attenuates the catecholamine response to CPB and surgery and has been associated with reduced AKI compared to a standard anesthetic technique. Volatile anesthetic agents have variable AKI effects in animals, but this has not been assessed in humans. Although CPB duration predicts AKI, there is conflicting evidence that CPB avoidance (i.e., off-pump) protects the kidney. Interpretation of retrospective studies comparing on and off-pump bypass procedures is often complicated by selection bias for off-pump patients having fewer renal risk factors making reduced AKI more likely. A meta-analysis of off vs. on-pump studies (20,845 patients), most of which were non-randomized, found reduced renal failure with off-pump. In contrast, a meta-analysis of 10 randomized off vs. on-pump trials (1467 patients) did not find a difference. Leukodepletion during CPB may reduce AKI. Minimally invasive surgery using catheter-based CPB (e.g., portaccess) has been associated with improved renal outcome for both mitral and aortic valve surgery. Early evidence suggests that the reduced AKI and mortality seen with endovascular stenting vs. surgery for abdominal aneurysms may also be relevant thoracic aneurysms.

Bypass management modifications have been investigated. Extreme CPB anemia (hematocrit less than 20%) is associated with postoperative AKI, but the alternative, transfusion, is also implicated. To avoid unnecessary transfusion, preoperative optimization (e.g., oral ferrous sulfate therapy, erythropoietin), intraoperative cell salvage and antifibrinolytic use, avoidance of unnecessary hemodilution and anemia tolerance is advocated, but the threshold for transfusion to minimize AKI and other adverse outcomes of cardiac surgery is controversial and an optimal target hematocrit yet to be determined. Hypothermia during CPB does not provide intraoperative protection for the kidneys. Lower flows during CPB, rather than lower mean blood pressures, predict AKI. While vasopressin may be preferable to conventional catecholamines for shock, the relative renal effects of these agents in cardiac surgery is not known.
In one study, so called “fast track” protocols were associated with increased AKI in high-risk cardiac surgery patients; changing back to conventional management was associated with renal failure rates returning to “normal.”

**Pharmacologic interventions**

**DA1 agonist agents**

A meta-analysis of 61 randomized “low-dose” (<5μg/kg/min, 3359 patients) dopamine renoprotection trials concluded there was no benefit regarding mortality, dialysis, or adverse events. Low dose dopamine was associated with a 24% increase in urine output on day 1, and small changes in serum creatinine (4% drop) and creatinine clearance (6% rise), effects that disappeared from day 2 onward. Other dopamine effects include added atrial fibrillation risk, impaired splanchnic oxygenation and gastrointestinal function, endocrine and immune dysfunction, and ventilatory drive blunting. Citing the numerous negative studies and undesirable side effects, some strongly worded editorials are highly discouraging of the use of dopamine for renoprotection, referring to this practice as “bad medicine” and “superstition.” Nonetheless, dopamine continues to be used in the treatment of AKI.

Current fenoldopam studies provide insufficient data to draw conclusions regarding renoprotection in humans although a recent metaanalysis suggests more research is needed. A study involving 80 high-risk cardiac surgery patients found no benefit. In a randomized trial of 160 cardiac surgery patients with baseline renal dysfunction, fenoldopam, but not placebo, was associated with a drop in creatinine and higher creatinine clearance values, averaged over the first five postoperative days. A randomized study of 155 critically ill but hemodynamically stable patients with established AKI found no reduction in death or dialysis. In a secondary analysis of only cardiac surgery patients a trend towards improvement was noted, but there were also concerns of a higher incidence of adverse outcomes in diabetic patients.

Dopexamine is a peripheral dopamine receptor and β2-adrenergic receptor agonist that binds to dopamine receptors in the kidney causing vasodilation. A systematic review of 21 randomized-controlled dopexamine trials found inconsistent and insufficient evidence to support any claims of renoprotection.

**Diuretic agents**

Diuresis does not assure improved renal function. Studies of loop diuretics (e.g., furosemide) in cardiac surgery patients have associated these agents with worse renal outcomes. Mannitol is commonly added to CPB circuit prime, but randomized and retrospective cardiac surgery studies do not confirm renoprotection. However, in some situations (e.g., suspected myoglobinuric AKI), mannitol-induced forceful diuresis may be of benefit. Natriuretic peptide hormones have been evaluated in human trials. Perioperative infusions of human recombinant BNP (Nesiritide) were shown to reduce AKI, shorten hospital stay, and improve 6 month survival in a single randomized study of 272 coronary bypass patients with impaired left ventricular function. However, this must be contrasted with non-surgical studies indicating that BNP may worsen renal function in heart failure patients. Renoprotection trials with human recombinant ANP (Anaritide) and renal natriuretic peptide (Urodilatin) have been inconclusive.

**Insulin**

Return of filtered glucose to the circulation by the kidney is an energy-consuming process. However, in a randomized study of 400 cardiac surgery procedures, there was no gain and even a trend towards higher stroke and mortality rates, with the addition of intensive intraoperative (target glucose 80-100mg/dl) vs. conventional (target <200mg/dl) glucose management.

**N-acetylcysteine**

N-acetylcysteine is a vasodilator with antioxidant properties. Complicating interpretation of N-acetylcysteine studies is its effect on serum creatinine independent of renal function. A review of the twelve meta-analyses evaluating studies of N-acetylcysteine therapy for contrast nephropathy concluded that the available data do not allow definitive conclusions. Several randomized N-
Acetylcysteine trials in high renal risk coronary bypass surgery patients have found no evidence of renoprotection.

**Sodium Bicarbonate**

Studies subsequent to a first randomized study of postoperative bicarbonate infusion that demonstrated promising results compared to saline have failed to support this therapy.

**α2 adrenergic agonist agents**

The normal physiology of the kidney includes α2-adrenergic receptor-mediated vasodilating effects. Preoperative clonidine was associated with reduced renal injury in one study of cardiac surgery patients. Despite supportive evidence for improved renal performance and survival benefit with α2 agonists, they are not commonly used for renoprotection.

**Other vasodilators**

A randomized trial found reduced AKI in 450 cardiac surgical patients receiving nitroprusside during CPB rewarming compared to control. Calcium channel blockers decrease renal vascular resistance and increase glomerular filtration. A meta-analysis of five randomized cardiac surgery studies involving 161 patients and four agents (diltiazem, verapamil, nifedipine, and nimodipine) found no effect on AKI or mortality compared to control or other agents (e.g., nitroglycerin, dopamine).

Insufficient data exists to evaluate the renoprotective properties of ACEI's and angiotensin 1 receptor blocker agents in cardiac surgery patients.

**Selected References:**