Learning Objectives:
1. To describe the risks of cardiac surgery associated acute kidney injury (AKI)
2. To identify etiologies for acute kidney injury after cardiac surgery
3. To examine current strategies for perioperative renal protection and salvage

The diverse sources of perioperative renal insult relevant to cardiac surgery are extensively reviewed elsewhere (Figure). Commonly, perioperative AKI represents a cumulative burden of insult from multiple sources including exacerbation of preexisting disease, ischemia/reperfusion, nephrotoxins, oxidative stress, and inflammation. Hypoperfusion, inflammation, and atheroembolism are well studied contributors to cardiac surgery-related AKI. Contrast dye is also an important insult as part of some hybrid procedures, and a variety of other contributors such as rhabdomyolysis related to an ischemic limb may be important for some patients. In addition, particular major vascular surgeries add renal risk due to the nature of the procedure, such as those involving circulatory arrest or temporary renal artery occlusion. In general, each patient assumes a cumulative burden of renal insult that combines with factors that influence vulnerability to injury such as genetic makeup to predict the kidney's response. Unfortunately, preoperative risk assessment alone anticipates only a small fraction of the variability observed in postoperative AKI. Two common primary pathways are thought to enact AKI-related renal cell death; these are irreversible injury due to ischemia-reperfusion and apoptosis related to activation of caspase “executioner” enzymes.

Low output states, cardiopulmonary bypass, hypovolemic shock, vasoconstrictor use, and circulatory arrest all may contribute to the renal ischemic burden of a surgery. Tissue disruption, endotoxemia from infectious or septic complications, transfusion, and cardiopulmonary bypass can serve as triggers for release of pro-inflammatory cytokines such as tumor necrosis factor alpha [TNF±] and interleukin 6 [IL-6].

Clamp occlusion and cannulation of the aorta are actions that can cause embolization by disrupting atheromatous plaque. Measures of cardiac atherosclerosis...
and intraoperative arterial emboli counts are strong independent predictors of AKI after cardiac surgery.\textsuperscript{4, 5} Embolic occlusion of renal vessels from dislodgement of atheromatous plaque can lead to segmental necrosis of an affected kidney. Surgical procedures on atherosclerotic vessels are known to have high particulate emboli rates (57-77\%),\textsuperscript{6, 7} and emboli showers are predictably high, for example, at the time of cardiac unclamping.\textsuperscript{8}

Upon close review of recent literature from both cardiac surgery and other settings, major advances in understanding of the pathophysiology of most types of organ injury have occurred, but while effective kidney protection therapies exist in some settings (e.g., rhabdomyolysis - mannitol), disappointingly little progress has been made with post-cardiac surgery AKI. Nonetheless, thoughtful summary of these data identify patterns that repeat by organ system, such that information that yields progress from one system is now being used to guide research efforts for others. Most advanced is myocardial protection, for which interventions have even been developed that are effective even after organ injury has begun.

While \textbf{prophylaxis} is highly effective for disorders such as postoperative infection where modifying conditions that are conducive to developing the complication is realistic (eg. antibiotics, glucose control, temperature); unfortunately similar approaches to prophylaxis for organ injuries such as perioperative AKI have not been effective. Examples include a myriad renoprotective agents (eg. dopamine, furosemide).

\textbf{Prevention} (or avoidance) comes in four major forms:

1) \textbf{Simple avoidance strategies}: For example, eliminating nephrotoxic agents such as specific antibiotics, aprotinin, or contrast dye (eg. by delaying surgery post-catheterization, or using TEE rather than venography to guide intraoperative catheter placement etc..

2) \textbf{Active avoidance strategies}: For example, employment of blood sparing strategies to reduce transfusion - these may decrease perioperative AKI by eliminating potential harmful side effects of transfusion and extreme anemia.

3) \textbf{Avoidance through procedure innovation}: Some minimally invasive procedures can achieve surgical goals with reduced organ insult. For example, evidence suggests that minimally invasive mitral and aortic valve surgeries can reduce AKI compared the equivalent procedure performed by median sternotomy incision. Interestingly, some procedure innovations expected to be beneficial provide little
or no evidence of organ protection (eg. off-pump CABG surgery) and/or may not meet success in achieving the original goal of the surgery.

4) Avoidance through radical reductions in organ energy consumption prior to a timed insult: The success of these interventions stems from combining simultaneous decreases in the organ function and metabolism rather than by completely eliminating the impact of an insult. Key to success of these strategies is detailed knowledge of the anticipated insult (ie. timing, duration, and mechanism). These interventions involve hypothermia (~15°C) +/- high potassium perfusion to attenuate the adverse effects of ischemia. to neutralize transmembrane electrical gradients. Examples include organ preservation for transplant. Unfortunately, hypothermia for cardiac surgery has never been shown to be useful for prevention of AKI.

**Treatment** of established organ injury is different from prevention of further ongoing injury and comes in two forms.

1) Prompt intervention to influence the course of an organ insult. Key to success of these strategies is immediate knowledge of the occurrence of an insult, and the tools to promptly intervene. An example is thrombolytic therapy for coronary or cerebral artery thrombosis. Prompt intervention requires early diagnosis, either by patient symptoms (eg. angina, hemiparesis), and/or early biomarker evidence (eg. CKMB, ST segment depression). In this regard, the absence of “renal angina” or any proven reliable early biomarkers is a major problem progressing AKI therapies.

2) Hastening recovery. While this has received considerable attention in terms of understanding the physiology of recovery, and even some clinical studies (eg. growth hormones), there are no currently clinically viable interventions for renal protection.

3) Temporizing while recovery occurs. This is an intervention of last resort in most cases, and relevant to kidney as dialysis replaces kidney function.

“Salvage” is not currently a clinically relevant strategy, but experimental evidence suggests that therapies such as inhibitors of apoptosis may have potential as future interventions.
In terms of the targets for intervention outlined above and postoperative AKI there are in fact some tools at hand that can allow achievement of surgical goals with reduced organ injury. However, if a narrow view of organ protection by pharmacologic protection is taken in the prevention of postoperative renal protection, then therapies supported by animal studies generally lack support from clinical studies (e.g., dopamine, furosemide). Characteristics of cardiac surgery related organ injury such as the heterogenous causes and relative lack of information as to onset make perioperative injury particularly difficult to defend against.

Nonetheless, current approaches to optimizing the drug development pipeline have been identified. Over the past several years, speculation on reasons for the lack of progress in perioperative organ protection has focused on various parts of the translational drug development pipeline. Key factors identified include the absence of consensus definitions to support comparisons among studies, disagreement on relevant organ protection endpoints, recurring deficiencies in clinical trial design such as inadequate sample size and the lack of validated early diagnostic tools to provide the best chance for drug effectiveness. Also cited, the need for an expanded role of information technology - untapped opportunities through database interrogation to better understand AKI and inform trial design. Finally, the poor track record of conventional animal models in identifying therapies that will translate into effective clinical therapies.

Despite steadily improving understanding of the time course and consequences of renal insults related to cardiac surgeries there has been very little progress in improving renal protection for these procedures.
References:


