Panel: Perioperative Renal Dysfunction and Outcomes
Title: Diuretics and Dopamine: What is the Evidence?
Author: Robert N. Sladen, MBChB, FCCM
Institution: Columbia University Medical Center, New York, NY 10032

Learning Objectives:
1. To review preventative strategies and treatment options for acute kidney injury (AKI) complicating cardiac surgery.
2. To examine the evidence basis for pharmacologic interventions, including osmotic and loop diuretics, dopaminergic agonists (dopamine, fenoldopam), and natriuretic peptides (ANP, BNP) in the patient at high risk for renal dysfunction undergoing cardiac surgery.

Pharmacologic Renal Protection

Osmotic and Loop Diuretics
Mannitol (25-50 g) is routinely added to the pump prime, although there are few clinical data that define its true role in renal protection during CPB. It does not prevent subclinical renal injury (microalbuminuria, tubular enzynmuria), but AKI after uncomplicated CPB in patients with previously normal renal function is rare. Mannitol increases urine flow during infra-renal cross-clamping but does not prevent intraoperative decreases in GFR. Postoperative osmotic diuresis can exacerbate hypovolemia and hypokalemia. Persistent inability to concentrate urine (isosthenuria) has been shown to be predictive of perioperative AKI.

Loop diuretics (furosemide, bumetanide, torsemide, ethacrynic acid) have long been used to “convert” oliguric to nonoliguric AKI. However, it is most likely that oliguric patients who respond to diuretics have a lesser renal injury than those who do not, with an intrinsically more favorable outcome. Moreover there is evidence that “forced” diuresis may exacerbate hypovolemia and renal injury. Once dialysis is required, high dose furosemide does not alter the natural history of AKI.

Dopaminergic Agonists
Dopaminergic agents (dopamine, fenoldopam) potentially confer renal protection by increasing renal blood flow (RBF), diuresis and saliuresis. By activating cyclic AMP they “turn off” the energy-dependent tubular sodium pump and thereby decrease tubular oxygen consumption; increased intratubular urine flow protects against tubular obstruction.

Low dose (1-3 µg/kg/min) dopamine, added to high dose furosemide and mannitol, can also convert oliguric to nonoliguric states if given within a few hours of injury. However there is little evidence that “prophylactic” low dose dopamine has any role in cardiac surgery. In part this may be because there is very wide variability in dopamine pharmacokinetics, i.e. some patients given low dose dopamine may achieve high plasma levels, i.e. in the beta- or alpha-adrenergic range. When oliguria is associated with slow heart rate and low blood pressure in a volume repleted patient, initiation of dopamine as an inotropic agent can be very helpful. However, its usefulness is limited by its propensity to induce supraventricular arrhythmias especially postoperative atrial fibrillation.
Fenoldopam is a phenol derivative of dopamine that is selective for the DA-1 receptor and lacks any beta- or alpha-adrenergic effects. There is considerable Level B and meta-analysis evidence that prophylactic perioperative administration at low doses (0.05-0.3 mcg/kg/min) can preserve GFR during and after CPB and decrease the incidence of AKI. However large randomized controlled trials (RCTs) are needed to define whether this benefit has any impact on outcomes such as requirement for renal replacement therapy (RRT), length of stay or mortality.

**Natriuretic Peptides**

The natriuretic peptides are formed by the endogenous synthesis of chains of 22-32 amino acids. They specifically oppose the sympathoadrenal, renin-angiotensin, aldosterone, and arginine vasopressin (AVP) systems, and induce vasodilation and natriuresis via activation of cyclic GMP. A-type (atrial) natriuretic peptide (ANP) is released by atrial stretch; B-type (brain) natriuretic peptide (BNP) is released by ventricular dilation. Assay of BNP (and its precursor, N-terminal-pro-BNP) is an established diagnostic tool for acute cardiac failure. C-type natriuretic peptide (CNP, great vessels) and urodilatin (kidney) are endogenous analogs.

Human recombinant ANP (anaritide) infusion during CPB significantly decreases renin-angiotensin and aldosterone responses, and preserves GFR. Preliminary data suggested that administration in patients with severe AKI it could decrease dialysis requirement and mortality. However, mortality was increased in nonoliguric patients, perhaps because the surviving nephrons are more sensitive to hypotension induced by ANP. A subsequent trial in oliguric patients showed no difference in outcome.

Human Recombinant BNP (nesiritide) is FDA-approved for the parenteral treatment of patients with advanced decompensated CHF (ADCHF). Infusion decreases cardiac preload and afterload, promotes diuresis and relieves pulmonary edema and anasarca. Considerable controversy was elicited by implications that nesiritide may adversely affect renal function in ADCHF. In a prospective, controlled study in patients undergoing coronary revascularization of mitral valve surgery with CPB, a perioperative infusion of nesiritide (0.01 mcg/kg/min) was associated with lower Scr and 6-month mortality. However no large RCT has been done to confirmed these preliminary observations.

**Non-diuretic Interventions**

N-acetylcysteine (NAC) is naturally occurring glutathione precursor and free radical scavenger. It is well established in the treatment of acetaminophen toxicity, and there is considerable experimental evidence of its effectiveness in ameliorating nephrotoxic AKI. When combined with hydration, prophylactic oral NAC (600 mg PO bid x 2 days) provides significant renal protection in radiocontrast nephropathy (RCN). However, NAC may decrease creatinine production and thereby give a false impression of the extent of its benefit.

No renal benefit has been demonstrated by the perioperative infusion of NAC during cardiac surgery. NAC must pass through the liver to be converted to glutathione, so in part this may be due to inadequate knowledge regarding the appropriate parenteral dose of NAC to protect against clinical IRI.

It is well established that urinary alkalinization (pH > 6.5) protects against tubular injury in myoglobinuria (rhabdomyolysis) as well as RCN. There is preliminary clinical evidence that urinary alkalinization can ameliorate AKI during cardiac surgery, but this needs to be substantiated by a large RCT.
Conclusions

Unfortunately, in 2013, there is no compelling evidence that any pharmacologic intervention can definitively prevent or attenuate AKI and alter patient outcome. An international foundation managed by the National Kidney Foundation (NKF) called Kidney Disease: Improving Global Outcomes (KDIGO) has generated guidelines on prevention of AKI (www.KDIGO.org). Their current recommendation is that diuretic therapy, low dose dopamine, fenoldopam or atrial natriuretic peptide should NOT be used to prevent or treat AKI. The question is, where do we go from here?

Selected References


