Kidney Medicine

Acute Kidney Injury Prevention Following Cardiac Catheterization: The Ins and Outs of Management

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Hydration remains a cornerstone of prevention strategies for contrast-associated acute kidney injury (CA-AKI) following cardiac angiography.[1] How hydration mitigates kidney injury is not clear. Correction of latent volume depletion with improved cardiac output and renal perfusion, dilution of contrast in the nephron, decreased contact time with epithelial cells, and enhanced medullary oxygenation may all play a role. However, the downside to aggressive infusion of fluid is precipitating heart failure, particularly in patients with underlying cardiac dysfunction.

A large body of literature reviewed[2] supports hydration therapy for the prevention of CA-AKI particularly when compared with no hydration.[3,4] In general, the more fluid given and the greater the urine output is, the lower the incidence of CA-AKI. To avoid precipitating heart failure with aggressive hydration therapy, some protocols reduce the rate and amount of hydration in patients with a history of heart failure or use some form of assessment of volume status to adjust the rate. Three trials using assessment of volume status to adjust hydration therapy consistently observed that those who received more fluid had a lower incidence of CA-AKI (Table 1).[5-7] Using this approach, there was no increase in heart failure in the group that got the most fluid whereas the incidence of CA-AKI was significantly reduced.

One could argue that the group that received the most fluid started out on the steeper part of the cardiac Starling curve. As such, they might have had the greatest increase in cardiac output and as a result renal perfusion. The enhanced renal perfusion might be the proximate cause for the reduced CA-AKI. Urine output too is likely to have increased in those who received the most fluid; however, this was not quantitated in the studies.

Two trials attempted to randomize patient to more or less hydration. Maioli et al[8] randomized patients to an early versus late start to fluid administration at a constant rate. Those randomized to the early start group received more fluid because it was given over a longer period of time. The early start group had a lower incidence of CA-AKI, but the interpretation of the results is confounded by timing.[8] The early start administration might have had a greater influence on correcting volume depletion, toning down vasoconstrictor neurohumoral factors, increasing urine output, etc.; however, no difference in the rate of CA-AKI between 2 groups randomized to different rates and durations of fluid administration was observed. However, despite one group getting 50% more fluid, there was no difference in urine output over 24 hours.[9] Regarding the role of hydration, A MAstricht Contrast-Induced Nephropathy Guideline trial has taken the issue to the extreme and compared rates of CA-AKI in those who received standard of care hydration with those that received no hydration. They found no increased incidence of CA-AKI in those who received no hydration. The patients were a mix of intravenous and intra-arterial contrast, and all were low-risk patients.[10] Although hydration plays a role in reducing the incidence of CA-AKI, these trials do not provide insight into a mechanism of action. This is where urine output may have a role.

In an observational trial by Stevens et al[11] that used a variety of strategies to specifically increase urine output in patients with chronic kidney disease undergoing cardiac angiography, the more urine that was produced over the 24 hours following contrast exposure, the lower the incidence of CA-AKI. The strategies included the use of intravenous fluids and diuretics with or without dopamine or mannitol. Fluid balance was not recorded. The authors found that an average urine output of 150 mL/h over the 24-hour period after contrast exposure was associated with no increase in serum creatinine. In the absence of fluid balance data, one cannot be sure about whether positive fluid balance might have masked some changes in creatinine because of hemodilution.

One approach to answering the question of importance of what goes in versus what goes out is to look at trials administering fluid that is not likely to increase preload and cardiac output. There have been a number of small prospective randomized trials comparing a prescribed amount of oral water with a prescribed amount of intravenous saline. Meta-analyses of these trials have found equivalence with respect to the incidence of CA-AKI.[12] A recent study found that ingesting >15 mL/kg following contrast exposure was the threshold for benefit.[13] Given that the effect of oral water is likely limited to inducing an increase in urine output but not intravascular volume expansion, the benefit of oral water suggests that what comes out might be most important.

An additional group of studies that administers isotonic fluid without attempting to increase intravascular volume provides further insights. Forced matched diuresis attempts to specifically increase urine output using loop diuretics and then replaces the urine loss with an equivalent amount of isotonic saline. An initial 250-mL bolus of saline precedes the matched diuresis period. This bolus has a relatively small effect on intravascular volume (60 mL or 2% increase). Furthermore, the whole process is started only 1 hour before exposure to contrast. Urine output using this approach usually increases to 300-600 mL/h for up to 6 hours following contrast

Table 1. Relationship Between Amount of Fluid Administered and Incidence of CA-AKI in Trials using Hemodynamic Monitoring to Determine the Amount of Fluid Administered

Group	Amount of 0.9% saline administered (mL)	Incidence of CA-AKI[a]
Poseidon Group 1	448-874	17%
Poseidon Group 2	874-1,512	11%
Poseidon Group 3	1,512-3,055	6%
CVP Group 1	500-1,000	38%
CVP Group 2	1,000-1,500	31%
CVP Group 3	>1,500	8%
Hydra Group 1	961-1,680	11%
Hydra Group 2	2,522-3,600	5%

Abbreviations: contrast-associated acute kidney injury; CVP, central venous pressure.
[a]CA-AKI defined as >0.3 mg/dL increase in creatinine in left ventricular end-diastolic pressure and bioimpedance vector analysis trials; CA-AKI defined as >25% or >0.5 mg/dL increase in creatinine in CVP trial. Data extracted from trials using left ventricular end-diastolic pressure (Poseidon), bioimpedance vector analysis (Hydra), and CVP.[5-7]

exposure, much more than is achieved with intravenous fluids alone. Using this approach, CA-AKI is usually reduced by about 50%.[14]

Forced matched diuresis has also been studied in patients undergoing transcatheter aortic valve replacement (a procedure that uses contrast) and cardiac surgery (no contrast) with significant reductions in the incidence of AKI.[14,15] Finally, a recent prospective trial randomized patients to left ventricular end-diastolic pressure-guided fluid administration rates versus forced matched diuresis. Superiority was found with forced matched diuresis (CA-AKI 5.7% vs 10%) again suggesting that what comes "out" may be more important than what goes "in".[16] In addition, there was less pulmonary edema in the forced matched diuresis group (0.3% vs 2.0%) despite this group receiving more fluid.

How increasing what comes "out" reduces the risk of CA-AKI is speculative. Under the right conditions of dose and time of exposure, contrast is directly toxic the renal tubule cell.[17] The incidence of CA-AKI is directly related to the density of nephrogram obtained immediately after the cardiac procedure.[18] Furthermore, forced matched diuresis is known to be associated with the absence of nephrograms postprocedure. This supports the idea that dilution of contrast and wash out from the nephron may be important mechanisms of the beneficial effects of higher urine outputs. However, this would not easily explain the benefit observed in patients undergoing coronary artery bypass graft unless another toxin such as free hemoglobin is a major mechanism of injury.[19] Alternatively, a high-urine output may have some other benefit.

Observations in man indicate that ingestion of 20 mL/kg of water leads to an increase in medullary oxygen content as detected using blood oxygenation level-dependent magnetic resonance imaging. The increase in medullary oxygen levels involves enhanced perfusion of the medulla mediated by prostaglandins and nitric oxide as it can be inhibited by nonsteroidal anti-inflammatory drugs and restored with nitric oxide donors.[20] The effect diminishes also with aging. Whether it is present also in those with comorbid conditions such as diabetes and hypertension is not clear. That an increase in urine output improves medullary oxygenation is an intriguing hypothesis that requires further confirmation.

In summary, hydration (the "in") can diminish the incidence of AKI following exposure to nephrotoxins such as contrast. The evidence suggests that a significant component of this benefit is mediated by an increase in urine output (the "out"). A greater "out" may dilute the nephrotoxin in the lumen of the nephron (decreasing exposure of renal epithelial cells) and increase renal microcirculation, particularly in the medulla of the kidney, enhancing oxygen delivery. This latter effect may involve decreases in the viscosity of the contrast (particularly isosmolar contrast) and vasodilation of the vasa recti vessels.

The concepts presented here are relevant in clinical practice. Protocols for the prevention of CA-AKI often specify a specific rate of fluid administration for a specific period of time before, during, and after exposure to contrast. This is a reasonable first step, but attention to urine output should also be incorporated into the protocol. Failure to achieve a urine output of, say, 100 mL/h should result in an alert. If the patient is not clinically volume depleted, a dose of furosemide might be administered.

As a practical approach, intravenous hydration should continue to be prescribed for all patients who are at "high-risk". This should be supplemented with oral fluid, which stimulates a more immediate increase in urine output. NPO (nothing by mouth) orders should be limited to a few hours before the procedure. Encourage patients to drink water liberally both before and after contrast exposure with a goal to producing a brisk output of colorless urine.

ARTICLE INFORMATION

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Financial Disclosure: Dr Solomon serves as a scientific advisor for RenalGuard with no financial relationship with the company.

Peer Review: Received October 3, 2023. Evaluated by 1 external peer reviewer, with direct editorial input from an Associate Editor and the Editor-in-Chief. Accepted in revised form February 26, 2024.

 Published online July 11, 2024 with doi 10.1016/j.xkme.2024.100865

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