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EDITORIAL COMMENT

# Improving Intravenous Fluid Therapy for Prevention of Contrast-Induced Nephropathy

## How to Give More Without Causing Heart Failure*

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Iodinated contrast media is widely used to enhance the image of organs and the vascular compartment. In a small percentage of patients, the administration of contrast is followed by a decrease in glomerular filtration rate (GFR), referred to as contrast-induced nephropathy (CIN). The fall in GFR is detected by a rise in serum creatinine evident within 48 to 72 h of contrast exposure. The decrement in GFR is usually transient, and serum creatinine returns to or near baseline levels within 7 to 10 days. CIN is, nevertheless, associated with in-hospital mortality and adverse events (1), long-term mortality (2), progression of kidney disease (3), long-term major adverse cardiovascular events (4), and reduced use of cardiovascular preventative medications (5).

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The mechanism of CIN is multifactorial and includes regional hemodynamic changes (6) as well as direct renal tubule cell toxicity (7). Patients at risk for CIN are usually older, receive more contrast, and have underlying compromised kidney and vascular function (chronic kidney disease, diabetes, heart failure). The setting in which contrast is administered is also important, with higher rates of CIN occurring with ST-segment elevation myocardial infarction, with transcatheter aortic valve replacement, and in hemodynamically compromised patients.

Preventative strategies for CIN can be employed because administration of contrast is a known event. A number of approaches to CIN prevention have been subjected to prospective randomized trials. The majority of these trials have been conducted in high-risk patients undergoing coronary angiography with or without a percutaneous coronary intervention.

The mainstay of preventative therapy is reduction in the amount of contrast administered. Additionally, intravenous (IV) administration of isotonic fluids before, during, and after contrast exposure is also considered standard of care. Potential mechanisms for the benefit of IV fluids include reductions in systemic and regional vasoconstrictor forces, improvement in tissue resistance to reactive oxygen species (8), and enhanced washout of contrast through the kidney. This latter effect is supported by observational data that the incidence of CIN is reduced with higher urine flow rate (9–11). Because increasing urine flow itself does not increase GFR and contrast clearance, it is assumed that the concentration of contrast within the tubule lumen is diminished and transient time through the nephron is increased by these high urine flow rates. This would mitigate the exposure of renal tubule cells to the direct toxic effects of the contrast.

It would thus make intuitive sense to just give as much isotonic fluid as possible to minimize the toxic effects of contrast and create enough volume expansion to turn down vasoconstrictor tone. Unfortunately, too much fluid can have a deleterious effect, particularly in patients with underlying impaired cardiac function, by provoking acute decompensated

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heart failure (ADHF). It is this goal to achieve efficacy without sacrifice of safety that drives attempts to find novel ways to guide therapy.

POSEIDON (Prevention of Contrast Renal Injury with Different Hydration Strategies) used left ventricular end-diastolic pressure (LVEDP) obtained before any contrast was given to determine a rate of IV fluid administration during and after the angiography. Compared with patients randomized to standard of care, patients randomized to IV fluid on the basis of LVEDP received twice as much fluid. The incidence of CIN was reduced in those patients (6.7% vs. 16.3%, relative risk: 0.41; $p = 0.005$) (12).

Two trials used a forced diuresis system (RenalGuard, Milford, Massachusetts) with IV fluid administration matching urine output drop by drop in real time. High urine outputs (300 to 600 ml/h) were achieved without a risk of ADHF. Both trials found a lower incidence of CIN with the RenalGuard device (9,10).

In this issue of *JACC: Cardiovascular Interventions*, investigators from China describe a strategy using dynamic central venous pressure (CVP) to guide the amount of IV isotonic saline administered before, during, and after coronary angiography (13). In a double-blind, randomized prospective trial, 264 patients were given 0.9% NaCl starting 6 h before the procedure and continuing for 12 h after the procedure. Patients were at high risk for CIN by virtue of a history of symptomatic ADHF, left ventricular ejection fraction <50%, and chronic kidney disease with estimated glomerular filtration rate 15 to 60 ml/min/1.73 $m^2$. The control group received 1 ml/min/h for the entire period (approximately 18 h). In the dynamic CVP group, the rate was adjusted hourly depending upon the CVP. The 2 groups were well matched for age, baseline left ventricular ejection fraction, estimated glomerular filtration rate, CVP distribution, and presence of diabetes. Percutaneous coronary intervention was carried out in 85% and 90% of patients, respectively, with an average contrast volume of 161 and 171 ml.

As one might expect, the dynamic CVP group received more IV fluid (1,827 ml vs. 1,202 ml) and had a greater urine volume (1,461 ml vs. 806 ml) during the study period. This translated into a significant reduction in CIN by any definition (15.9% vs. 29.5% using a definition of >25% and/or >0.5 mg/dl increase in creatinine). There was no benefit in the dynamic CVP group when the initial CVP was >12 $cmH_2O$, and patients received the identical IV infusion rate as control subjects. When analyzing all 264 patients as a single group, the rate of CIN fell significantly as the amount of IV fluid given increased. No patients developed CIN who received >1,700 ml over the study period.

The reduction in the incidence of CIN was also associated with a reduction in 90-day major adverse events. Only 9 patients required cessation of IV fluid for symptoms of ADHF (4 control, 5 CVP), and 52 patients in the CVP group required a reduction in IV fluid rate.

These results reaffirm the importance of giving as much IV fluid as possible for prevention of CIN. The results also reaffirm indirectly the association of a high urine flow rate with a reduced risk of kidney injury. Using CVP or LVEDP aids in maximizing the amount of IV fluid without risking ADHF. An alternative approach is forced diuresis using RenalGuard that does not induce a change in extracellular volume.

Despite these encouraging results, the incidence of CIN has not dropped to zero, suggesting that mechanisms unaffected by volume expansion or urine output are contributing to kidney injury following contrast administration. This creates space for additional novel therapies to be explored.

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