Prediction and Prevention of Contrast Nephropathy

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Among those with diabetes for 25 years or more, the prevalence of diabetic nephropathy in type 1 and type 2 diabetes is 57% and 48%, respectively. The U.S. epidemic of obesity, the aging population, and improved treatments for diabetes, renal disease, and cardiovascular disease are expected to be the principal drivers of a secondary epidemic of diabetic nephropathy with its renal and cardiac sequelae. Although acute radiocontrast nephropathy (RCN) requiring dialysis occurs in less than 1% of the percutaneous coronary intervention (PCI) population, lesser degrees of renal dysfunction occur in approximately 15%.[1] Even small degrees of renal dysfunction in the post-PCI period are related to increased morbidity and mortality. Despite advances in PCI care, including stents and advanced antithrombotics, the risk of RCN remains unchanged over the last decade.

Multiple studies have confirmed that the single most important factor for predicting RCN is the baseline renal function. Unfortunately, the serum creatinine (Cr) in mg/dL is a crude indicator of glomerular filtration rate. A better measure is the creatinine clearance (CrCl), which can be calculated using the Cockcroft-Gault formula:

$$\text{CrCl} = [140 - \text{Age (yrs)} \times \text{weight (kg)}/[\text{serum creatinine (mg/dL)} \times 72].$$

$$\text{ClCr}_{\text{Male}} = 1 \times \text{CrCl}$$

$$\text{ClCr}_{\text{Female}} = 0.85 \times \text{CrCl}$$

Acute renal failure requiring dialysis can be predicted from baseline CrCl and diabetic status, given an anticipated contrast volume of 250 mL for a combined diagnostic angiogram and PCI, with substantial risks beginning at a CrCl of 30 mL/min and lower.[1] Of note, it has been shown that even transient dialysis has a similar 6-month prognosis to permanent dialysis, with an 80% mortality rate.[1]

Various agents have been investigated in the prevention of RCN. Essentially, all prophylatic regimens can be placed into three categories: maintenance of urine output, improvement of renal hemodynamics, and reduction of direct toxicity of contrast agent. Of the 35 interventional trials performed to prevent RCN, few strategies have proven to be beneficial besides hydration, forced diuresis with volume replacement, and use of low-ionic contrast.[2,3] However, it is important to mention that most showing no effect or that were in conflict with other trials were underpowered to find significant benefit should it have existed. To make things more complex, those trials that were positive were not powered to find the main effect observed, were based on small number of endpoints, and occurred in protocols leading many to believe the findings were due to random error. For example, Tepel et al reported a 90% event reduction in 83 patients randomized to prophylactic acetylcysteine given orally or hydration prior to contrast computed tomography.[4] This effect size is almost certainly a reflection of statistical variation due to small number of endpoints (10 total for the trial). In support of random error and not treatment effect is the large event rate in the control group, 21%, which is not consistent with the contrast load or risk of the subjects.

Today, fenoldopam mesylate, a selective dopamine-1 receptor agonist, has been shown to significantly increase renal blood flow in those undergoing contrast procedures, hence counterbalancing one of the principal drivers of ischemic injury, intra-renal vasoconstriction.[5,6] A recent, multicenter, double-blind, randomized trial was performed with fenoldopam given 0.1 μg/kg/min starting 60–90 minutes prior to, and continued for 4 hours after exposure, in 45 patients undergoing angiography with a mean Cr level of 2.6 mg/dL. In this trial, renal vasoconstriction was inferred from para-amino-hippurate (PAH) clearance at baseline and 1 hour after contrast exposure. Fenoldopam was found to completely reverse the vasoconstriction: +15.8% versus –33.2% change in PAH clearance with hydration alone. As a result, fenoldopam blunted the rise in Cr from 2.64 to 2.77 versus 2.62 to 3.55 mg/dL, $P < .01$. Although not powered for a binary endpoint, fenoldopam reduced the incidence of RCN (defined as a 0.5 mg/dL rise in Cr) from 41% to 21%, $P = .15$. These preliminary data have been the critical foundation for CONTRAST, the pivotal, placebo-controlled, randomized trial of fenoldopam in approximately 300 patients with CrCl < 50 mL/min. The design of this trial has been challenging, given the fact that fenolopam may have a narrow therapeutic window where there is renal vasodilatation without hypotension.

Over the last 10 years, the main advances in RCN have come in our ability to predict outcomes for an individual patient. Treatment trials have been nearly uniformly disappointing. Recent positive, pilot studies with fenoldopam will require confirmation in the pivotal CONTRAST Trial. In the meantime, adequate prehydration and maintenance of post-PCI urine flow rates of >150 mL/min remain the most prudent measures. As the population ages, breakthroughs with respect to new contrast agents or effective prevention measures will be needed to offer PCI to the spectrum of patients at risk for renal injury. ■

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