Contrast-Associated Acute Kidney Injury
Will Clarifying Mechanisms Allay Anxiety?

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Iodinated contrast has long been regarded as an iatrogenic nephrotoxin. Concern about contrast-associated AKI has impelled clinicians to deploy a number of preventive strategies, especially for patients deemed to be at high risk. This includes volume expansion with isotonic saline before, during, and after exposure to contrast. Sensitization to the risks of contrast-associated AKI has propelled the development of safer contrast agents with lower osmolality and the deliberate minimization of delivered contrast volumes (1). Although more difficult to objectively measure, the fear of inducing AKI may influence clinicians to defer or avoid vital contrast-based investigations and procedures, potentially to the detriment of patients. These evolving selection and preventive practices may explain, in part, why more recent observational studies have not demonstrated an association between intravenously administered contrast exposure and AKI, which has led some to question whether contrast agents are actually nephrotoxic (2).

The clinical relevance of contrast-associated AKI, traditionally defined as a serum creatinine rise of 25% or 0.5 mg/dl occurring approximately 2–5 days after contrast exposure, has also been a source of controversy. Although the decrements in kidney function that define contrast-associated AKI are associated with adverse events such as mortality, cardiovascular events, and kidney failure, there is an appreciation that such relationships are highly confounded (3). This has led to a concerted effort to evaluate the effect of strategies intended to mitigate contrast-induced nephrotoxicity on outcomes that are more relevant to patients. As a result, recent trials in this area, and in the wider arena of AKI, have increasingly adopted major adverse kidney events (MAKE), a composite outcome encompassing the receipt of dialysis and/or some degree of sustained loss of kidney function and often death (MAKE-D), as their primary end point (4,5).

Translational research can inform the debate on the clinical significance of contrast-associated AKI by shedding light on the mediators of this phenomenon. Several mechanisms may explain contrast-mediated kidney injury, including direct toxicity to tubular cells, intrarenal vasoconstriction, and oxidative stress. Recognizing the limitations of serum creatinine as a marker of tubular damage, investigators have sought to examine the trajectory of biomarkers reflective of tubular injury after contrast exposure. Previous studies have reported that serum and urinary neutrophil gelatinase-associated lipocalin (NGAL) and urinary IL-18 levels anticipated contrast-associated AKI in patients exposed to intra-arterial iodinated contrast (6,7).

In this issue of CJASN, Liu et al. conducted a comprehensive assessment of novel biomarkers among 922 (18%) participants in the landmark Prevention of Serious Adverse Events Following Angiography (PRESERVE) trial, a 2 × 2 factorial randomized controlled trial of isotonic sodium bicarbonate versus normal saline and N-acetylcysteine versus placebo to prevent MAKE-D at 90 days in patients undergoing intra-arterial angiography (4,8). The PRESERVE trial mandated that all participants have some degree of CKD (eGFR < 15–60 ml/min per 1.73 m² for participants with diabetes and 15–45 ml/min per 1.73 m² for those without diabetes) in order to enrich the cohort with individuals who would be at higher risk of contrast-associated AKI and downstream adverse events. The investigators sought to clarify whether biomarkers of kidney injury (neutrophil gelatinase-associated lipocalin, kidney injury molecule-1 [KIM-1], and IL-18) and repair (monocyte chemoattractant protein-1, YKL-40, and uromodulin), measured both in plasma and urine, were associated with contrast-associated AKI. Samples were drawn at baseline and at 2–4 hours after angiography. Participants in the substudy were broadly representative of the larger trial cohort, which comprised predominately White men with diabetes. Median baseline eGFR was 50 ml/min per 1.73 m². The most common contrast-based procedure was a diagnostic coronary angiogram. The primary outcome of interest for this substudy was the development of contrast-associated AKI (increase in serum creatinine of ≥25% or ≥0.5 mg/dl) on the basis of serum creatinine changes from baseline to 3–5 days after angiography. Contrast-associated AKI and MAKE-D occurred in 7.9% (8.9% in the full PRESERVE trial) and 6.5% (4.5% in the full PRESERVE trial) of participants, respectively.

Patients who experienced contrast-associated AKI did not have a larger pre-to postangiography rise in any of the biomarkers of interest when compared with individuals who did not have contrast-associated AKI. For reasons that are not clear, all of the plasma biomarkers had a nonstatistically significant downward trend after
angiography in both patients with and without contrast-associated AKI. Similarly, there was no pre-to postangiography change in any biomarker among patients who experienced MAKE-D versus those who did not. The authors concluded that the majority of contrast-associated AKI events could be better explained by contrast-induced changes in kidney hemodynamics rather than intrinsic tubular damage.

Several intriguing insights can be derived by examining the association between some baseline biomarker levels and the subsequent development of contrast-associated AKI and MAKE-D. Plasma KIM-1 concentrations, for example, were already higher before angiography in patients who would eventually experience these events. This is consistent with data on KIM-1 from studies of patients with CKD. Among patients with type 1 diabetes, elevated serum KIM-1 was associated with more rapid CKD progression (9). Previous work from the Chronic Renal Insufficiency Cohort showed that in patients with CKD, higher urinary KIM-1 concentrations were independently associated with heart failure, cardiovascular events, and death (10). This would suggest that KIM-1, and other biomarkers that were independently associated with MAKE-D, anticipated a higher risk of short- and long-term postangiography events that was distinct from any toxicity mediated by contrast exposure. Future trials testing interventions in the CKD population may leverage the baseline concentrations of these biomarkers to better enrich the population with patients at higher risk of important clinical events.

Liu et al. have completed the largest study to comprehensively utilize biomarkers of cellular injury and repair in order to better understand the pathophysiology of contrast-associated AKI. The study was embedded in a rigorously performed randomized trial with meticulous data collection and outcome ascertainment. Urine and plasma samples were collected, processed, and stored using a well-defined protocol across the 19 participating sites.

The results of this study must be interpreted with some caveats. Samples were acquired 2–4 hours after angiography, which could have been too early to detect bona fide contrast-induced cellular damage. Although the PRESERVE trial enrolled patients who were at high risk of adverse events, the majority of patients had eGFRs >45 ml/min per 1.73 m², and individuals with unstable kidney function, active heart failure, or those requiring urgent angiography were excluded. The majority of patients received diagnostic coronary angiograms, which may entail a lower risk of complications than interventional procedures. All patients received optimal preventive therapy including reasonable volumes of isotonic fluids and modest contrast loads. About 90% of patients who experienced contrast-associated AKI had stage 1 AKI using the Kidney Disease: Improving Global Outcomes classification. Thus, the conclusion that direct tubular injury does not mediate contrast-associated AKI needs to be contextualized. One cannot rule out the possibility that in a higher-risk population undergoing more complex interventions with larger contrast volumes, biomarker evidence of tubular injury would not be found. Additionally, most of the patients were white men, thereby limiting the generalizability of the findings to other demographic groups.

The work of Liu et al. and the wider PRESERVE trial provide important insights into the contemporary state of contrast-associated AKI. The low frequency and minimal severity of contrast-associated AKI in the PRESERVE trial reflect years of progress in preventing contrast-associated AKI and mitigating the effect of contrast-mediated nephrotoxicity. In the few patients who did develop contrast-associated AKI, the absence of a “biomarker signal” suggests that most patients with modest creatinine increases after angiography suffer only a marginal insult. A recent analysis of the PRESERVE cohort reminded us that the majority of patients who developed contrast-associated AKI did not go on to experience a MAKE-D event (11). This information should provide clinicians with confidence to refer similar patients for diagnostic and therapeutic procedures involving the use of iodinated contrast, with an understanding that even if the serum creatinine concentration rises modestly after the procedure, the implications are likely of limited clinical relevance. Nonetheless, it would be premature to discount the toxicity of iodinated contrast in patients with severe underlying kidney disease or those who require more complex contrast-based interventions. Future studies in such populations using novel biomarkers are needed to broaden our understanding of whether and how iodinated contrast damages the kidney.

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See related article, “Postangiography Increases in Serum Creatinine and Biomarkers of Injury and Repair,” on pages 1240–1250.