Biomarkers in Contrast-Induced Acute Kidney Injury

By Steven D. Weisbord, MD, MSc

Contrast-induced acute kidney injury (CI-AKI) is a common condition that is associated with serious, adverse short- and long-term outcomes. Despite substantial advancements in our understanding of CI-AKI, the capacity to effectively risk-stratify patients, diagnose incipient renal injury before elevations in serum creatinine (sCr) manifest, and identify patients at highest risk for adverse downstream events is limited. Blood and urine biomarkers of kidney injury hold promise as a means by which the risk-stratification, diagnosis, and prediction of progression of CI-AKI could be significantly enhanced, and the judicious implementation of cost-effective preventive care and treatment to mitigate adverse outcomes substantially improved.

Renal tubular injury in CI-AKI, which results from medullary hypoxia, generation of reactive oxygen species, and direct tubular toxicity of contrast media, occurs almost immediately following contrast administration. In a rat model of CI-AKI, Liss et al. (1) demonstrated a reduction in outer medullary renal blood flow within minutes of contrast administration, with the most pronounced decrement occurring within 10 to 20 minutes. Bakris et al. (2) documented increased oxygen free radical generation within 5 minutes and reduction in glomerular filtration of nearly 50 percent less than 20 minutes following contrast administration in dogs. Hofmann et al. (3) demonstrated that medullary blood flow in healthy human subjects decreased within 20 minutes following intravascular contrast administration. These and other studies confirm that the adverse hemodynamic and nephrotoxic effects of iodinated contrast develop within minutes following contrast administration. However, the diagnosis of CI-AKI in clinical practice is based on identifying elevations in sCr that typically manifest days following contrast administration. Consequently, provider and patient awareness of the development of CI-AKI is delayed or may not occur at all if follow-up assessment of sCr is not performed. As a result, supportive care to mitigate kidney damage, including correction of intravascular volume depletion and withdrawal of potentially nephrotoxic medications, may be delayed or not implemented. This lag in diagnosis underscores the strong need to identify other blood and/or urine markers that are sensitive and specific for early renal tubular injury, that identify patients with CI-AKI at the time of initial kidney insult, and that help inform the provision of appropriate care to attenuate the risk for progressive kidney damage.

Figure 1. Pathophysiology of contrast-induced acute kidney injury and timing of events

Prior studies of biomarkers in CI-AKI

Over the past decade there have been many studies investigating biomarkers for the risk stratification, diagnosis, and long-term prognosis of AKI. These studies focused largely on renal injury in the postoperative and intensive care unit settings. The predictive, diagnostic, and prognostic capacity of biomarkers in the context of iodinated contrast administration has been less well characterized. However, the studies that have been conducted to date demonstrate the potentially important role biomarkers may play in the setting of CI-AKI (Table 1) (4–15).

Table 1. Studies of biomarkers and contrast-induced acute kidney injury

Nakamura et al. (11) demonstrated that preangiography urinary liver fatty acid binding protein (L-FABP) levels were higher among patients who developed CI-AKI than patients who did not (18.5±12.8 μg/g vs. 7.4±4.9 μg/g; p<0.01). Postangiography L-FABP levels increased among patients with CI-AKI, yet remained unchanged in patients without CI-AKI (46.8±30.5 μg/g vs. 8.0±6.2 μg/g; p<0.001). A subsequent study by Hirsch (8) demonstrated higher concentrations of urine neutrophil gelatinase-associated lipocalin (NGAL) (155±32 ng/mL vs. 11.6±3 ng/mL; p<0.001) and plasma NGAL (151±34 ng/mL vs. 36±4 ng/mL; p<0.001) 2 hours following angiography in patients with CI-AKI compared to patients without CI-AKI. Urine and plasma NGAL at 2 hours were strong independent predictors of CI-AKI (p<0.0001, respectively). In a study of 150 patients, Ling et al. (9) demonstrated that in addition to diagnosing kidney injury earlier than sCr, urine interleukin-18 (IL-18) levels 24 hours postangiography predicted the development of major adverse cardiac events over 17 months of follow-up (relative risk [RR] =2.09; p=0.001). More recently, in a study of 410 patients with CKD undergoing angiography, Briguiori et al. (13) demonstrated that elevations in serum cystatin C (CyC) of ≥10 percent at 24 hours were 100 percent sensitive and 86 percent specific for the development of CI-AKI and were predictive of 1-year death and need for dialysis. Moreover, this threshold increase in serum CyC was more predictive of 1-year death and need for dialysis than elevations in sCr.

Notwithstanding these promising preliminary findings, there are certain methodological limitations to these studies. First, a large proportion of patients did not have baseline CKD, which is the principal risk factor for CI-AKI; consequently only a small minority developed CI-AKI. Second, since biomarker levels may be affected by baseline kidney function, the generalizability of findings from many of these studies to subjects with baseline CKD is not clear. Third, most studies did not track longer term outcomes. Thus, little is known about the ability of biomarkers to predict progressive kidney disease and other adverse events following CI-AKI. Lastly, several studies examined just one bio-
marker rather than a panel of biomarkers, limiting the capacity to determine if combinations of biomarkers are more predictive than a single biomarker. Notwithstanding these limitations, the findings of these studies suggest that biomarkers could potentially improve the ability to risk stratify patients, diagnose early CI-AKI, and identify risk for serious, adverse longer term sequelae.

CI-AKI is a common condition associated with adverse outcomes. Notwithstanding advancements in our understanding of risk factors for, pathophysiology of, and potential adverse events associated with CI-AKI, there remain significant limitations in our capacity to effectively and efficiently prevent, treat, and limit longer term effects of CI-AKI. Preliminary studies of blood and urine biomarkers in the setting of contrast administration suggest that biomarkers may be a means by which the care for patients at risk for and with CI-AKI could be improved. Large, well-designed studies that measure panels of biomarkers and that provide the opportunity to investigate “yet to be identified” biomarkers are needed to inform the delivery of evidence-based, effective care for the prevention and treatment of this iatrogenic condition.

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Disclosure

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References