Acute Kidney Injury After Cardiac Angiography and Exposure to Iodinated Contrast Media

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A 75-year-old female patient with a history of chronic kidney disease stage IV, type 2 diabetes mellitus, hypertension and dyslipidemia presented to an outside hospital with a 3-day history of substernal chest pain that radiated to her jaw and the left side of her back. An electrocardiogram showed a slight ST elevation in the anterior leads, so she was subsequently transferred to our hospital. Before transfer, she received ticagrelor, aspirin and heparin.

Her medications before the transfer included losartan, hydrochlorothiazide, simvastatin, acetylsalicylic acid and insulin. On admission to our hospital, she was awake and alert, with a blood pressure of 160/77, a heart rate of 82, and an oxygen saturation of 97% on room air.

She was found to have a serum creatinine of 1.96 (baseline 1.9–2.5 over the past year) that correlated with an eGFR of 25 ml/min. Her sodium and potassium concentrations were 138 mEq/l and 4.2 mEq/l respectively. Her troponin I was 1.6.

The diagnosis of ST-segment elevation myocardial infarction prompted the initiation of an emergent cardiac catheterization. She underwent revascularization with drug-eluting stents. During the procedure, 100 ml of low osmolar contrast (Isovue 370, Bracco Diagnostics Inc., Princeton, NJ) was used. She was stable post-procedure. A nephrology consult was requested to help manage a potential contrast-induced acute kidney injury.

Post catheterization, the patient appeared to be slightly volume overloaded with bibasilar rales and bilateral 2+ lower extremity edema. She received 1 dose of intravenous furosemide post-procedure and produced more than 1 L of urine output. The patient was otherwise stable hemodynamically, with a minimal supplemental oxygen requirement. Losartan and hydrochlorothiazide were held.

Eighteen hours after percutaneous coronary intervention (PCI), her serum creatinine was 2.24 mg/dl; it had increased to 3.34 mg/dl at 42 hours. Her urine output decreased from 2900 ml in the first day of admission to 300 ml in the next day. Furosemide 40 mg oral 2 times daily was started on day 2 of admission, but the patient had no increase in urine output. Her weight was stable.

Her serum creatinine peaked at 65 hours post-PCI at 3.36 mg/dl (Figure 1). Clinically, the patient was hemodynamically stable. The patient was discharged on the same day on a low-sodium diet. A follow-up serum creatinine 4 days later was 2.56 mg/dl.
Discussion

This patient represents a classic example of acute kidney injury that occurred after cardiac angiography and exposure to iodinated contrast media. Contrast media are water-soluble organic molecules that contain iodine and are excreted almost entirely by the kidneys, with a half-life measured in a few hours.

First described in 1954, what we now call contrast-induced acute kidney injury (CI-AKI) is defined by a change in serum creatinine that follows a characteristic course (see Figure 1). Creatinine begins to rise usually within 24 hours of exposure and peaks on day 3 or 4 before slowly returning to or close to the baseline value over the next 7–10 days. Other explanations for a change in creatinine must first be excluded.

The threshold increase required for a definition of CI-AKI varies in the literature from a relative increase of 25% to an absolute increase of 0.5 mg/dL. These definitions produce different incidences of CI-AKI in the same population, making it difficult to compare studies on prevention. Among patients undergoing cardiac angiography, the incidence of CI-AKI is ~5% but can increase to more than 50% in some high-risk patients. In patients undergoing contrast-enhanced computed tomography exams, the incidence even in patients with chronic kidney disease appears less often and depends on the setting (inpatient versus outpatient) and whether severe renal dysfunction is present.

The Acute Kidney Injury Network (AKIN) group has proposed a new definition of acute kidney injury as an absolute 0.3 mg/dL increase in creatinine within a 48-hour period, or a decrease in urine output to less than 0.5 mg/kg/h and sustained for at least 6 hours despite corrective measures. This definition is just beginning to gain acceptance in the cardiology and radiology literature.

Pathophysiology

Contrast media are nephrotoxic to the kidneys through at least two mechanisms. First, all contrast media decrease blood flow to the kidney, particularly in the medullary portion of the kidney. Studies of isolated descending vasa recta, the main vessels supplying oxygen to the tubules in the medulla, indicate that contrast media cause vasoconstriction mediated by the generation of reactive oxygen species and a decrease in availability of nitric oxide. This causes an ischemic injury in this portion of the kidney. Additional mechanisms of injury occur through direct toxicity to the cells lining the renal tubules. This injury also generates reactive oxygen species and proapoptotic stimuli, leading to loss of cell viability.

The contrast effects on vasa recta and tubule cells result in a decrease in glomerular filtration rate (GFR) and, thus, a rise in creatinine. The toxicity of contrast is not directly on the glomerulus, and the decrease in filtration is a response to the downstream damage to the tubule through a process called tubuloglomerular feedback (TGF). Although the change in GFR occurs early in the course of CI-AKI, it takes days for enough creatinine to be retained in the body to reach the threshold for a diagnosis of CI-AKI. Newer injury markers analogous to a renal troponin, such as NGAL, KIM-1, and IL-18, will hopefully permit earlier diagnosis of this injury.

Consequences of CI-AKI

CI-AKI is a specific form of injury to the kidney. Evidence that acute kidney injury of any etiology leads to an accelerated loss of kidney function is just beginning to be appreciated. Both small prospective studies and retrospective analyses of large databases indicate that patients who develop CI-AKI progress to worse kidney function over the ensuing years compared to those without CI-AKI.

In the short-term, CI-AKI increases hospital length of stay, in-hospital mortality and overall cardiovascular mortality over the following 5 years. Are these adverse events caused by the CI-AKI, or are patients who develop CI-AKI already destined for worse outcomes because of their comorbid conditions and the burdens of risk factors? The answer to this question is of great importance and the subject of ongoing study.

Prevention of CI-AKI

Because the administration of contrast is predictable and the consequences of CI-AKI are significant, efforts to prevent this form of kidney injury are indicated. Knowledge of the pathophysiology of CI-AKI has led to a number of strategies.

The first step is identifying which patients are most likely to suffer CI-AKI. Patients with decreased kidney function before contrast exposure are at higher risk because each remaining nephron must excrete a greater load of the contrast, thus increasing the potential for toxicity. Any condition that compromises renal blood flow at baseline will further increase the risk. For example, patients with congestive heart failure, volume depletion, current NSAID use and a limited ability to generate nitric oxide (such as patients with diabetes) are all at some increased risk. Patients with hemodynamic instability at the time of angiography — particularly those requiring supportive measures, such as the use of pressors or an intra-aortic balloon pump — are at increased risk. Finally, the more contrast agent used, the greater the CI-AKI risk. A scoring system to calculate not only the incidence of CI-AKI but also the need for renal replacement therapy has been in use for a number of years.

Once a high-risk patient has been identified, the next step is to minimize the modifiable risk factors. Volume-depleting agents (diuretics) and NSAIDs should be held and intravenous fluid administered. Although some controversies exist regarding the type, amount, and duration of IV fluid, most recommendations include normal saline at 1 ml/kg/h for 4–6 hours before and 12 hours after cardiac angiography. The amount can be increased to 3 ml/kg as a bolus for urgent/emergency cases, and modified to 1.5 ml/kg bolus in the presence of the symptoms of congestive heart failure. The use of IV fluid has now been incorporated into the latest guideline from the American Heart Association/American College of Cardiology (AHA/ACC). However, despite the use of IV fluid, the incidence of CI-AKI in high-risk patients remains ~10%.

The central pathophysiologic role of ischemia and the generation of reactive oxygen species have led to the use of antioxidant therapy as a strategy to prevent CI-AKI.
N-acetylcysteine (NAC) is a scavenger of reactive oxygen species and a precursor of glutathione, a natural antioxidant. Although initial studies suggested a preventive effect, subsequent prospective randomized trials and summary meta-analyses have diminished enthusiasm for this approach. As with any therapy, dose becomes critical, and a soon-to-begin trial will use a high dose administered for a longer duration (NCT01467466).

The use of isotonic sodium bicarbonate as the IV infusion fluid instead of sodium chloride was proposed based on the importance of acid pH in the generation of some reactive oxygen species. Because urine is generally acidic, administration of sodium bicarbonate to alkalize the urine was initially found to reduce the incidence of CIAKI. As with NAC, subsequent studies have reported mixed results, although meta-analyses still suggest a benefit. One multicenter trial using a higher dose of bicarbonate to ensure urinary alkalization is ongoing (NCT00930436).

A variety of approaches to inducing vasodilation in the kidney have met with limited success. Atrial natriuretic peptide, dopamine receptor agonists, prostaglandin E2, theophylline, endothelin antagonists and adenosine antagonist have all been studied in man or animal models, but have yet to gain any clinical traction.

Novel approaches to preventing CIAKI have included extracorporeal cooling of the patient, use of a coronary sinus catheter to remove contrast before it reaches the systemic circulation, and hemodialysis or hemofiltration to remove contrast. The only reported success has been with hemofiltration, in which Ringer’s lactate (a source of bicarbonate) is given at 1 l/h as an isovolemic replacement fluid for the ultrafilterate of plasma that is removed. A recent additional approach has been the induction of a high urine flow rate (300–800 ml/h) by real-time ml/ml replacement of urine output after a saline bolus (250 ml) and dose of furosemide (0.25 mg/kg). Two large European trials have reported success with this approach, which presumably dilutes the contrast in the renal tubule. A US trial with this device recently got under way (NCT01456013). Finally, a recent trial reporting a benefit of a novel approach, which presumably dilutes the contrast in the renal tubule. A US trial with this device recently got under way (NCT01456013). Finally, a recent trial reporting a benefit of a novel approach, which presumably dilutes the contrast in the renal tubule.

Finally, the choice of contrast media has been a controversial theme in the study of CIAKI. The first cases of CIAKI occurred with high osmolar contrast (~1500 mOsm/kg). When low osmolar contrast (~600–700 mOsm/kg) became available, comparative trials found a lower incidence of kidney injury in high-risk patients with the lower osmolar agents. This naturally led to the hypothesis that the osmolarity of the contrast determined nephrotoxicity. The more recent availability of iso-osmolar contrast (~290 mOsm/kg) and an initial positive comparative trial of iso-osmolar versus low osmolar contrast fueled this hypothesis. However, subsequent prospective randomized trials have failed to replicate the original findings, and meta-analyses also found no difference in the incidence of CIAKI between iso-osmolar and low osmolar contrast. The AHA/ACC 2011 guidelines reflect this lack of difference. Regardless of which contrast medium is used, every effort should be make to minimize the amount of contrast administered.

Summary
CIAKI reflects injury to the kidney and risk for cardiovascular events, mortality, subsequent progression of chronic kidney disease, and the need for dialysis. Patients at greatest risk can be identified in advance, and most institutions take steps to minimize the risk, such as using isotonic fluid administration and antioxidants, and minimizing use of contrast. Specific protocols to risk stratify and treat patients undergoing contrast administration have been shown to improve patient outcomes. New and novel approaches to prevention continue to be investigated.

References
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