Contrast-Induced Acute Kidney Injury

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Case Presentation: A 63-year-old man with prior mitral valve repair, hyperlipidemia, hypertension, and mild chronic renal insufficiency (creatinine 1 year earlier, 1.2 mg/dL) presents to the emergency department with progressive dyspnea on exertion and new anterior T-wave inversions. Subsequent laboratory testing confirms a myocardial infarction (troponin I, 11.0 ng/mL) and worsening renal insufficiency in the setting of recently being started on chlorthalidone for hypertension (creatinine, 2.7 mg/dL). Diuretics are discontinued; intravenous fluids are infused; and therapy for an acute coronary syndrome, including aspirin, clopidogrel, nitrates, and intravenous unfractionated heparin, is initiated. After 48 hours, creatinine improves to 1.8 mg/dL (estimated glomerular filtration rate, 46 mL/min), and the patient undergoes cardiac catheterization with iopamidol (Isovue, Bracco Diagnostics Inc, Princeton, NJ) contrast after receiving 1 hour of prophylactic sodium bicarbonate infusion. A complex bifurcation lesion of the left anterior descending artery/first diagonal branch is identified (Figure 1A). What is this patient's risk of contrast-induced acute kidney injury (CI-AKI), and which measures may modify that risk significantly? This Clinician Update reviews the recent literature on the acute kidney injury that follows the administration of iodinated contrast medium.

Risk Factors

Patients at risk for CI-AKI have comorbidities that will exacerbate the primary pathogenesis of the injury: contrast-induced vasoconstriction leading to diminished blood flow to the renal medulla. These comorbidities include diabetes mellitus, congestive heart failure, acute hypotension (requiring pressors or intra-aortic balloon pump), ST-elevation myocardial infarction, and volume depletion. Patients with chronic kidney disease are also at risk for contrast-induced acute kidney injury because compensatory mechanisms to maintain filtration function are diminished, and a smaller number of nephrons must excrete the contrast load. Procedural issues such as the amount of contrast administered[1,2] and the type of contrast administered[3] remain additional risk factors. Risk factor scoring (including both baseline comorbidities and procedural factors) has been used to predict the incidence of CI-AKI, need for renal replacement therapy, and long-term mortality.[4,5]

Incidence

Contrast-induced nephropathy will occur in 2% to 25% of patients undergoing coronary intervention.[4] The incidence of CI-AKI depends on the cohort studied and the definition used to identify those with kidney injury. The most common definition of CI-AKI is a rise of serum creatinine of 0.5 mg/dL or a 25% relative rise in creatinine at 48 hours after contrast exposure. Because accumulation of creatinine is relatively slow, it requires 48 to 72 hours to identify many cases of CI-AKI. Evaluation of creatinine at 24 hours after contrast exposure only will allow identification of the majority of patients who ultimately will develop CI-AKI and have adverse events.[6]

More rapidly increasing markers of glomerular filtration rate such as cystatin C have been used in some trials and may allow more accurate estimation of CI-AKI incidence at the 24-hour time point. Smaller changes in serum creatinine also identify individuals with poor outcomes and have been adopted for other forms of acute kidney injury.[7] These small changes such as an absolute increase of 0.3 mg/dL in serum creatinine permit earlier identification of kidney injury[8] and poor outcome in patients undergoing coronary angiography.[9] Other kidney

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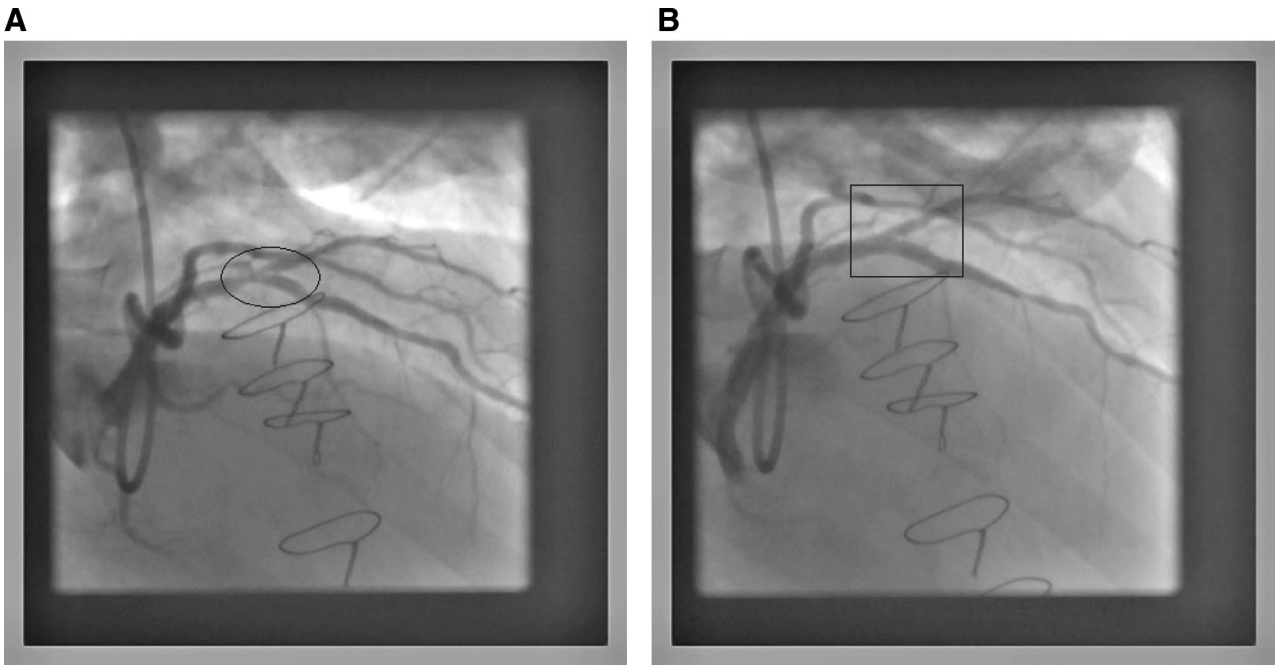

Figure 1. A, A complex culprit lesion in the left anterior descending artery (LAD) and first diagonal branch (D1). B, After 250 cm^3 iopamidol contrast dye, successful drug-eluting stent placement in the LAD-D1 bifurcation lesion.

injury biomarkers are in development, and some show promise as very early markers of kidney injury.[10,11]

When the more conventional definition of CI-AKI (25% relative or 0.5-mg/dL rise in creatinine at 48 hours) is used, patients can be risk stratified for the development of CI-AKI on the basis of comorbidities (estimated glomerular filtration rate <60 mL $\cdot$ min^{-1} $\cdot$ 1.72 m^{-2}, diabetes mellitus, congestive heart failure) and procedural variables (contrast volume, requirement for intra-aortic balloon pump).[4,5] Such a scoring system can predict a post–percutaneous coronary intervention range of CI-AKI from a rate of 7% for those at lowest risk to a rate of $>50\%$ for those with the highest risk score.[4]

Impact/Outcome

The occurrence of CI-AKI has been associated with poor short- and long-term outcomes, including death resulting primarily from cardiovascular causes.[12] It has been assumed by many that CI-AKI identifies patients with a greater burden of comorbidity and that the long-term adverse outcomes in patients who develop CI-AKI reflect that burden. This is analogous to the development of bleeding complications after coronary intervention. The association with increased mortality has been assumed by some to reflect comorbid conditions[13]; other data suggest that bleeding itself leads to increased risk of death regardless of comorbidities.[14,15] Recent prospective randomized trials in which an intervention reduces both the incidence of CI-AKI and long-term adverse outcomes raise the possibility that CI-AKI may directly contribute to an increased risk of cardiovascular and renal adverse events.[9,16] Episodes of acute kidney injury predispose patients to long-term loss of kidney function.[17] Long-term follow-up of patients who develop CI-AKI confirms that they experience a greater fall in glomerular filtration rate compared with individuals who do not experience CI-AKI.[18] Chronic kidney disease is a strong risk factor for cardiovascular events.[19] This additional perspective on the relationship between CI-AKI and long-term adverse events provides further rationale for prevention and for the development of new strategies.

Prevention of CI-AKI

Our understanding of CI-AKI pathophysiology suggests a complex interplay between vascular and tubule effects, making it unlikely that a single intervention will always be successful. The recognition of high-risk subgroups for CI-AKI and the possibility that CI-AKI plays a causal role in long-term increased risk of cardiovascular events mandate implementation of strategies to minimize the risk of CI-AKI.[20] Interventions with potential efficacy in reducing CI-AKI incidence are discussed here in the context of both their mechanism of action and current supporting clinical data.

Tubule Toxicity

Decreasing the concentration of contrast media within the tubule lumen and its contact time may diminish the direct toxicity of the contrast media. Thus, strategies to increase urine output before, during, and after contrast media exposure are used in high-risk patients. A higher urine output is associated with a lower incidence of CI-AKI.[21]The RenalGuard system stimulates a brisk urine output without changes in extracellular volume, and

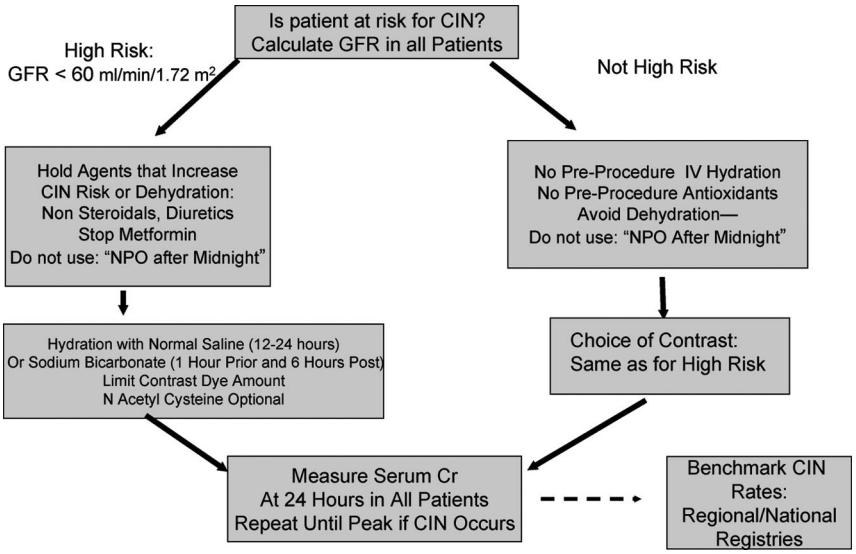

Figure 2. A sample algorithm for risk stratification, potential prevention, and assessment of CI-AKI occurrence. CIN indicate contrast-induced nephropathy; NPO, nothing by mouth; and GFR, glomerular filtration rate.

preliminary data support the protective role of high urine output.[22] However, inducing a high urine output with diuretics in the absence of adequate fluid replacement is deleterious.[23]

Generation of Reactive Oxygen Species

Both renal tubule cells and the vasa recta may be sources of reactive oxygen species. Antioxidants such a *N*-acetylcysteine (NAC) and ascorbic acid protect the tubule cell from apoptosis related to these reactive oxygen species.[24] In large animal models, administration of high-dose intracoronary NAC blunted the rise of serum creatinine by >50% and decreased renal tubule cell apoptosis.[25] Unfortunately, multiple clinical trials have documented the variability in efficacy of the antioxidants, NAC, and ascorbic acid. Human studies with NAC have generally required oral administration of the agent starting 24 hours before contrast media exposure. Evidence suggests that higher doses (total of 6000 mg over 48 hours) are required for high-risk patients (those with chronic kidney disease and/or congestive heart failure).[26] A few trials have used intravenous NAC with divergent results.[27] Meta-analyses have confirmed heterogeneity in these trials related to publication bias, dose of the agent, cohort studied, and definition of outcome.[27,28] Thus, it is not possible at this time to either recommend or dismiss antioxidants such as NAC for the prevention of CI-AKI.

A similar inconsistency in effect has been seen in trials using sodium bicarbonate. Sodium bicarbonate hydration improves urinary alkalinization, as opposed to normal saline hydration, which presumably works by decreasing the concentration of contrast media in the renal tubules. Urinary alkalinization may, like other antioxidant therapies, prevent CI-AKI via an effect on reactive oxygen species, namely inhibition of the generation of hydroxyl radicals from H_2O_2.[29] The advantage of the bicarbonate hydration approach is that it can be used essentially at the time that patients are headed into the catheterization laboratory. The initial trial gave intravenous isotonic sodium bicarbonate beginning 1 hour before and 6 hours after contrast media exposure.[30] The efficacy of this approach requires that the urine be alkalinized.[31] Subsequent negative trials have shown variability in the dose of bicarbonate and have not demonstrated sufficient urinary alkalinization to clearly compare outcomes among studies. Thus, although recent meta-analyses suggest a benefit for routine bicarbonate use for inhibition of reactive oxygen species to prevent CI-AKI,[32] the definitive multicenter trial has not yet provided an unequivocal strategy. A large, industry-sponsored, multicenter randomized renal failure outcome trial (Bicarbonate or Saline Study [BOSS]) comparing high-dose bicarbonate and normal saline in patients at high risk for CI-AKI is currently enrolling, with results expected in 2011 (http://www.clinicaltrials.gov; unique identifier: NCT00930436).

Reversal of Medullary Blood Flow Reduction

Attempts to improve medullary blood flow with systemic administration of vasodilators have been consistently unsuccessful (reviewed by Kelly et al[33]). These efforts have been confounded by systemic hypotension (which would increase the risk of kidney injury), preferential vasodilation in the renal cortex (which might "steal" blood from the hypoxic medulla), and nonspecific stimulation of both vasoconstrictor and vasodilator receptors. An attempt to minimize systemic hypotension by direct infusion of fenoldopam into the renal arteries has shown some promise in a proof-of-concept trial[34] and an observational database.[35]

Choice of Contrast Agent

The chemical characteristics of contrast media responsible for nephrotoxicity are not known, although both osmolality and viscosity have been associated with physiological effects that might contribute to kidney injury. However, in recent clinical trials, these characteristics do not seem to be discriminatory. A number of randomized trials have compared iso-osmolar, high-viscosity contrast with low-osmolar, low-viscosity contrast with varying results. Recently, the Cardiac Angiography in Renally Impaired Patients (CARE) trial randomized 414 patients at high risk for CI-AKI to angiography with either iopamidol or iodixanol; no difference in any mea-

sure of CI-AKI could be discerned between these 2 groups.[36] Meta-analysis of these trials[3,37] supports equivalent safety of iso-osmolar and low-osmolar contrast, with the possible exceptions of ioxaglate and iohexol.[38]

Strategy

Prevention of CI-AKI requires the identification of patients at risk, elimination of those factors that could increase risk, application of an intervention to minimize risk, and appropriate follow-up to determine whether CI-AKI occurred and, if so, to address the long-term adverse outcomes (Figure 2). Given the possibility that CI-AKI is not simply a "transient, benign creatinopathy" but rather a direct cause of worsening chronic renal function and increased cardiovascular events, institutions should now consider prevention of CI-AKI a quality improvement goal. Despite the lack of clarity of prevention strategies, clinicians can develop an approach that is simple, used consistently by operators, and practical.[20] While we await conclusive data from randomized clinical trials, the efficacy of institutional algorithms in preventing CI-AKI can be prospectively addressed via national and regional registries. These observational studies can provide real-time feedback on a variety of complications, which should include the rate of contrast-induced nephropathy.

Case Resolution

The patient was successfully treated with a drug-eluting stent in the proximal to mid left anterior descending coronary artery and a provisional T stent in the diagonal branch (Figure 1B). This complex coronary intervention was performed with 250 cm^3 iopamidol contrast. After the procedure, intravenous bicarbonate was infused for 6 hours, and diuretics were not reinstituted. After 48 hours, the creatinine was 1.3 mg/dL (estimated glomerular filtration rate, 57 mL/min), and the patient was discharged home on dual antiplatelet therapy without further cardiorenal events.

Disclosures

Dr Solomon consults for Bracco Diagnostics Inc, PLC Med, and MD Sci Inc. Dr Dauerman consults for MD Sci Inc.

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