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PRO/CON DEBATE

Con: Contrast-induced nephropathy—should we try to avoid contrast media in patients with chronic kidney disease?

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ABSTRACT

The incidence of acute kidney injury (AKI) attributed to iodinated contrast has been over-estimated and this has led clinicians to withhold potentially life-saving diagnostic and therapeutic interventions. There is mounting evidence that iodinated contrast plays only a minor role in the development of AKI in comparison with more significant risk factors such as pre-existing renal dysfunction, hemodynamic instability and exposure to nephrotoxic drugs. We will present data which challenge the dogma of avoiding iodinated contrast in patients with reduced renal function. Based on a rational and individualized risk-benefit analysis, we believe it is preferable to utilize iodinated contrast if alternate diagnostic or therapeutic options are comparatively ineffective or hazardous.

Keywords: acute kidney injury, angiography, contrast-induced nephropathy, creatinine, creatinine clearance

SHOULD IODINATED CONTRAST BE AVOIDED IN PATIENTS WITH IMPAIRED RENAL FUNCTION?

To begin the discussion, consider the following two clinical scenarios. A 60-year-old man with diabetes and chronic kidney disease with a serum creatinine (SCr) of 1.8 presents to the emergency room (ER) with a differential diagnosis that includes acute mesenteric ischemia. Computed tomography (CT) scan with iodinated intravenous contrast is the preferred diagnostic test to determine the etiology of abdominal pain and guide therapeutic intervention per the American College of Radiology appropriateness criteria [1]. Should iodinated contrast be withheld? Also consider a 70-year-old man who presents with an ST-elevation myocardial infarction (STEMI). The patient's comorbidities include hypertension, diabetes and an SCr of 2.1 mg/dL. He is on vasopressors to maintain a systolic blood pressure of 100 mmHg. Should coronary catheterization or intervention be avoided in favor of management that does not require iodinated contrast? In both cases, it is our opinion that the clinician should choose the optimal treatment as the additional risk of acute kidney injury (AKI) due to iodinated contrast is outweighed by the benefit of the treatment.

Since the first description of contrast-induced acute kidney injury (CI-AKI) in the 1950s, CI-AKI has incited clinician anxiety and frequently led to irrational deviations from optimal patient management strategies [2]. Accumulating evidence demonstrates that iodinated contrast may not be as menacing to renal function as previously believed. Although it is not disputed that iodinated contrast possesses some direct renal toxicity, it is often erroneously blamed for all cases of renal dysfunction following its administration in lieu of other contributors to AKI. AKI is most often caused by a combination of factors including dehydration, sepsis, hypotension, nephrotoxic drugs, advancing age, diabetes, arterial disease and preexisting renal dysfunction.

The reported incidence of CI-AKI varies from the single digits to >50%. The described incidence is dependent on multiple factors, including how CI-AKI is defined, the specific patient population of interest, the volume or chemical composition of the contrast agent and a variety of procedure-specific factors. Also contributing to the wide variation in the published incidence of CI-AKI is the near-uniform absence of a control group with risk factors comparable to the group receiving iodinated contrast. It is virtually impossible to design a prospective randomized trial due to the ethical considerations of withholding critical diagnostic and therapeutic options [3–6]. Patients who receive contrast often have a multitude of other independent risk factors for AKI, either from their primary pathology or comorbid diseases, independent of contrast administration.

In the absence of exposure to iodinated contrast, AKI is common in hospitalized patients. Based on a recent analysis of nearly 20 000 annual hospitalizations at an academic medical center, Mehran *et al.* [7] reported that the rate of AKI was 22.7% and AKI was associated with a more than 4-fold increase in mortality. Using the Nationwide Inpatient Sample, Wilhelm-Leen *et al.* reported the overall rate of AKI in hospitalized patients was not increased in patients receiving iodinated contrast (5.5 versus 5.6%, P = not significant) [3]. Zealley *et al.*

reviewed over 9000 general surgical patients and attempted to demonstrate an association of iodinated contrast and risk of AKI. The overall rate of AKI was 10.9% but this was not statistically associated with iodinated contrast [8]. Finally, Newhouse *et al.* examined the frequency and magnitude of renal function change in >30 000 hospitalized patients not exposed to iodinated contrast. They concluded that AKI was relatively common and clearly related to baseline renal function, and the adverse effect of contrast was likely overestimated [9]. These results are typical of other recent reports, showing a significant risk of AKI in hospitalized patients but failing to prove a causal relationship to iodinated contrast.

For >30 years, there have been reports that suggest intravenous administration of iodinated contrast is associated with negligible risk of AKI. In a now-classic report in 1985, Cramer *et al.* reported that the rate of AKI following head CT was not increased by administration of iodinated contrast (60–350 mL of iodinated contrast) [10]. Six years later, Heller *et al.* reported a similar inability to validate an association of iodinated contrast administration for CT scan with renal impairment [11]. To compensate for the absence of a control group, propensity score and risk analysis tools have been used with some success. McDonald *et al.* applied a propensity scoring method to 12 500 patients receiving both contrasted and non-contrasted CT scans, demonstrating no increased risk of developing AKI after iodinated contrast [12]. In a later study, the same group reported that intravenous iodinated contrast was not an independent risk factor for subsequent dialysis or mortality (80–200 mL of iodinated contrast) [13]. Hinson *et al.* examined the rates of AKI over a recent 5-year period at a single large academic emergency department (80–120 mL of iodinated contrast) [14]. Contrast administration for CT scans was not associated with an increased risk of AKI, chronic kidney disease, dialysis or renal transplant at 6 months [14]. Similarly, Davenport *et al.* examined emergency department CT scans over a 10-year period and found no significant difference in AKI, either with or without contrast exposure in patients with a glomerular filtration rate >30 mL/h (117 mL average of iodinated contrast) [15]. These findings strongly support a policy of ordering iodinated contrast-enhanced CT scans based on clinical indications.

Intravenous and intra-arterial contrast injections appear to have differing impacts on renal function. Although it stands to reason that contrast injected upstream of the renal artery will result in a higher concentration at the nephron than venous injection, other factors such as instrumentation to the renal arteries and thromboembolism make differentiating the causal factors of AKI difficult. Recently, Tong *et al.* [16] directly compared intravenous administration of contrast for CT scans with intra-arterial administration during cardiac catheterization. In over 1900 patients, they demonstrated no increased risk of AKI due to the mode of contrast administration (201 mL average for intra-arterial and 120 mL average for intravenous) [16]. Another study comparing intravenous CT angiography and intra-arterial contrast found no significant difference in the incidence of AKI (170 mL intravenous versus 230 mL intra-arterial iodinated contrast) [17].

In the coronary literature, there is increasing evidence that factors other than iodinated contrast play a dominant role in the development of AKI after coronary intervention. Johannes *et al.* reported that the incidence of AKI was 18% in consecutive patients in the Bremen STEMI Registry (148.5 mL mean of iodinated contrast) [18]. Of note, the severity of the STEMI and its hemodynamic sequela (e.g. hypotension, need for intra-aortic balloon pump) were predictive of AKI but there was no association between amount or type of iodinated contrast and the risk of AKI. The development of AKI was associated with a markedly increased risk of 30-day and 1-year mortality. Optimal percutaneous coronary intervention (PCI) was independently associated with a reduced risk of AKI, lending further support to the theory that the adverse hemodynamic consequences of myocardial infarction play a more significant role in the development of AKI than previously estimated. Caspi *et al.* reported no difference in the incidence of AKI in propensity score-matched STEMI patients treated with or without PCI (8.6% versus 10.9%, $P = 0.12$, 150 mL median volume of iodinated contrast) [19]. They concluded that AKI was chiefly related to older age, baseline renal dysfunction, heart failure and hemodynamic instability, and this was not demonstrated with iodinated contrast exposure. The previous studies did not show an independent association of iodinated contrast administration and AKI, and they are noteworthy as they have included adequate control groups with risk factors for AKI similar to the treatment groups.

When making the clinical decision to administer iodinated contrast, it is of utmost importance to consider the individual risk factors along with the specific procedural and contrast related risk factors to evaluate if the test or procedure will benefit the patient. Patient-related risk factors for contrast nephropathy common across all venues are chronic kidney disease, diabetes mellitus, advanced age, anemia, hypotension, hypovolemia, critical limb ischemia, obesity and critical tissue ischemia [5, 20]. In terms of procedural risk factors, the use of high volumes of contrast and procedural hypotension may contribute to the AKI [21]. It has been long demonstrated that high osmolality or highly concentrated contrast also contributes some additional risk of AKI [22]. A CT angiogram of the abdomen and pelvis uses 100 mL of iodinated contrast in our institution, this is slightly more volume than in standard contrasted CT exams and has caused providers reluctance in ordering this exam. Considering past over-estimation of contrast induced nephropathy (CIN) and the patient's disease process, the benefit to this patient is significant and early diagnosis will encourage timely treatment that may improve the outcome.

Acknowledging recent literature, it appears that the previously reported rates of CI-AKI have been overestimated. Newer research demonstrates that AKI is more often related to patient disease processes and procedural risk factors, which may not be directly correlated with iodinated contrast administration. If an individualized risk–benefit analysis favors the use of iodinated contrast administration, it is prudent to proceed with the intervention. In patients who possess multiple risk factors for AKI, elective procedures should be preceded by prehydration

and all nephrotoxic medications should be held. The use of non-contrasted studies should be exhausted before a contrasted study is performed. However, in the acute setting, optimization is often not feasible, and the minimal risk of CI-AKI should not discourage appropriate therapy. We believe that liberalizing the use of iodinated contrast to aid in patient management should be strongly considered, as iodinated contrast likely adds a negligible risk of AKI.

CONFLICT OF INTEREST STATEMENT

None declared.

(See related article by Windpessl and Kronbichler. Pro: Contrast-induced nephropathy—should we try to avoid contrast media in patients with chronic kidney disease? *Nephrol Dial Transplant* 2018; 33: 1317–1319)

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