The conundrum of contrast-induced acute kidney injury

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Abstract: More than sixty years have elapsed since contrast induced nephropathy (CIN) was first described in the medical literature. This term has since been extensively explored, with a variety of studies conducted to investigate its incidence and various mechanisms examined to explain its pathophysiology. However, the topic of CIN remains one of controversy with a widely variable and often questionable incidence derived from various studies. The past two decades have seen a surge in reports questioning the existing of CIN altogether and if more harm is actually being caused to patients out of fear of this potential complication. We have attempted to review relevant studies regarding CIN and highlight the key points of its surmised understanding. The review has a higher focus on more recent literature and updates, in order to determine if an accurate estimate can be made on the incidence of CIN. While there was certainly no lack of material available, practically all the studies reviewed were limited by one or more significant drawbacks that limited the reliability of their conclusions regarding CIN. Based on the information reviewed, the strengths and the flaws encountered in other studies can be used to design a randomized control trial that may help in concluding the longstanding debate on this topic. However due to time, financial, and perhaps even ethical constraints such a trial will be difficult to arrange, and so a definitive answer on CI-AKI, and whether it really exist, may continue to elude clinicians.

Keywords: Radiocontrast media; acute kidney injury (AKI); outcomes

Background

Medical imaging plays a pivotal role as an important diagnostic and therapeutic tool in the management of patient care in an era of great technological advances. Radiocontrast media are increasingly used to better enhance imaging in diagnostic computed tomography (CT), procedures of interventional radiology and percutaneous coronary intervention (PCI). The use of radiocontrast media, however, is not without side effects. One of the common complications with intravascular radiocontrast media exposure is the development of an acute kidney injury (AKI), first described in the 1950s in a patient with multiple myeloma (1,2). Since then, thousands of research papers related to contrast-induced acute kidney injury (CI-AKI) in both experimental and clinical studies have been published (3-10).

Indeed, CI-AKI is the third most common cause of hospital acquired AKI, representing about 12% of the cases, surpassed only by renal hypoperfusion (42%) and postoperative renal injury [18% (11)]. In most patients, CI-AKI may be transient and reversible in nature, although it has also been reported to be associated with increased long-term mortality in several studies (9,10,12). Recently, several research manuscripts have shown that radiocontrast media use may not be associated with AKI as similar rates of AKI were shown in patients who underwent contrast enhanced CT compared with those who underwent

Table 1 Proposed pathophysiological mechanisms of contrast-induced acute kidney injury [adapted from reference (25)]

Medullary vasoconstriction and hypoxia
Direct cytotoxicity to renal tubular cells
Release of vasoconstrictive mediators: Endothelin, adenosine, angiotensin II, vasopressin
Reduction of vasodilatatory mediators: Nitric oxide, prostocyclin
Increased oxidative stress
Impairment of tubulo-glomerular feedback
Increased blood and renal tubular viscosity
Impairment of mitochondrial function and mitochondrial membrane potential

unenhanced CT imaging (13-15). Thus far, it is not clear if CI-AKI is directly a cause of increased long-term mortality or merely a marker of high-risk patients, such as those with AKI or preexisting chronic kidney disease (CKD). Initial studies of AKI following intravenous (IV) radiocontrast media were limited by the lack of control groups and/ or did not adjust for additional covariates associated with AKI development. More contemporary studies have used propensity score–analyses to minimize selection bias, although without a prospective, randomized controlled trial, bias cannot be further eliminated.

Definition and epidemiology

There is no uniform definition of CI-AKI and this has hampered comparisons across studies. Traditionally, CI-AKI was diagnosed based on two measurements of serum creatinine levels [before and after radiocontrast media exposure (4,16-20)]. The most accepted definition was an absolute ($\geq$0.5 mg/dL) or a relative 25% increase in baseline serum creatinine concentration, assessed at 48 to 72 hours after a radiological procedure (18). This definition has been shown to correlate well with major adverse events and mortality on follow up studies. Of note, the diagnosis is notably one of exclusion and can only be made if AKI cannot reasonably be attributed to another etiology.

The incidence of CI-AKI has been reported to be >2% in the general population, however, the incidence increases to 20% to 40% in high-risk patients, for example, in patients with diabetes, congestive heart failure, CKD and older age. Each year, there are approximately 150,000 patients with CI-AKI reported in the world, and at least 1% requiring dialysis and prolonged hospital stay with increased cost of care and morbidity (5-10,12,21,22). The entity of CI-AKI was coined in association with coronary

angiography, despite 90% of all intravascular radiocontrast media being administered intravenously during CT studies. In a large national study, AKI incidence in patients hospitalized with acute myocardial infarction declined significantly from 2000 to 2008 despite the aging population and rising prevalence of AKI risk factors, where the reported AKI incidence declined from 26.6% in 2000 to 19.7% in 2008 (P<0.001) amongst patients who were admitted with acute myocardial infarction (23). However, these findings likely reflected increased clinician awareness, better risk stratification, or greater use of AKI prevention efforts during this time period.

Nevertheless, factors associated with more than doubling in the rates of CI-AKI and significant increases in the risk of AKI requiring dialysis include ST-segment elevation myocardial infarction (STEMI), eGFR <30 mL/min/1.73 m^2, and cardiogenic shock (24). Mehran *et al.* proposed a CI-AKI risk stratification score, where an increasing score number conferred an exponentially increased CI-AKI risk (16). The variables included in the CIN risk score were: (I) patient-related characteristics (i.e., age >75 years, diabetes mellitus, chronic congestive heart failure, or admission with acute pulmonary edema, hypotension, anemia, and CKD); and (II) procedure-related characteristics (i.e., the use of elective intra-aortic balloon pump or increasing volumes of contrast media). Increasing score numbers of $\leq$5, 6 to 10, 11 to 16, and $\geq$16 conferred an increasing CI-AKI risk of 7.5%, 14.0%, 26.1%, and 57.3%, respectively.

Pathophysiology

Several factors are related to the pathogenesis of CI-AKI (*Table 1*), comprised of hemodynamic changes of renal blood flow which causes hypoxia in the renal medulla, direct toxic effect of the radiocontrast media on renal cells associated with renal endothelial

dysfunction, and altered microcirculation (19,26-38). The administration of radiocontrast media leads to vasoconstriction, markedly affecting renal parenchymal oxygenation, especially in the outer medulla. After the injection of the high-osmolar ionic agent sodium iothalamate, cortical Po_2 declined from 40 to 25 mmHg, and the already hypoxic outer medulla, Po_2 fell from 26 mmHg at baseline to mean levels as low as 9 mmHg (39). A comparable decline of medullary Po_2 from approximately 30 to 15 mmHg with the administration of ionic and nonionic low-osmolar radiocontrast agents, as well as iso-osmolar dyes has also been described (40). In addition, neurohumoral mediators such as nitric oxide, plasma endothelin, adenosine, prostaglandin and vasopressin likely contributed further to the changes in renal microcirculation. Mechanical factors involving viscosity also played a role in the complex system causing low-pressure medullary microcirculation. An increased plasma viscosity after radiocontrast media administration has been demonstrated to interfere with blood flow, particularly within the hypertonic environment of the (inner) renal medulla, where the plasma viscosity is already increased. Indeed, there are several animal studies that have shown a correlation between experimental CI-AKI and viscosity of the radiopaque compound (35,36).

Evidence also suggested direct tubular toxicity on the proximal tubular cells from radiocontrast media, where there is an induced decline in tubule K^+, adenosine triphosphate (ATP), and total adenine nucleotide contents, and an increase in Ca^{2+} content (38). These changes were more pronounced with the very high-osmolality ionic compound than with the lower osmolality nonionic compound. The cytotoxic effects were aggravated by hypoxia, indicating interactions between direct cellular mechanisms and vasoconstriction-mediated hypoxia (36,37).

Literature review

Recent observational studies have raised questions on the prevalence and severity of CI-AKI following IV radiocontrast media, while other studies exploring the same subject have remained inconclusive due to the absence of control groups and adjustment with covariates associated with AKI. Indeed, prospective, randomized controlled trials published were performed to study the beneficial effects of different contrast materials used or prophylactic measures to prevent the development of CI-AKI, rather than addressing the question of the incidence of CI-AKI.

Furthermore, many interventions used to prevent CI-AKI may have had direct effects on the pathogenesis of AKI. For instance, the ability of volume expansion agents to decrease CI-AKI could be related to the hemodilution of serum creatinine level and correction of hypotension and viscosity in the medullary circulation. Many of the observational studies included data only from hospitalized patients, leading to selection bias toward a sicker population with multiple comorbid conditions associated with observed AKI independent of radiocontrast media exposure.

Numerous prospective and retrospective studies were unable to show increased rates of AKI in patients who received radiocontrast media (14,15,41). A recent meta-analysis of 28 observational controlled studies involving 107,335 participants demonstrated that when compared with non-contrast CT, contrast-enhanced CT was not significantly associated with AKI [odds ratio (OR) 0.94; 95% confidence interval (CI): 0.83 to 1.07 (42)]. A systematic review and meta-analysis of controlled studies examining the incidence of AKI in patients exposed to radiocontrast media compared with patients who underwent an imaging examination without radiocontrast media or were otherwise unexposed (control group) of 13 nonrandomized studies representing 25,950 patients demonstrated a similar incidence of AKI, dialysis, and death between the contrast medium group and control group (43).

Wilhelm-Leen *et al.* sought to estimate the burden of AKI among 5.9 million hospitalizations among adult patients receiving radiocontrast, as compared to patients with similar comorbidity and severity of illness who did not receive radiocontrast during their hospitalization. Patients who received radiocontrast did not develop AKI at a clinically higher rate—the rates of development of AKI were 5.5% (radiocontrast administered) *vs.* 5.6% (no radiocontrast exposure). After controlling for comorbidity and acuity of illness, radiocontrast media administration was associated with an OR for AKI of 0.93 [95% CI, 0.88 to 0.97 (44)]. When adjusted for age, sex, mechanical ventilation, and comorbidity, the administration of radiocontrast was correlated with a 7.4% (95% CI, 2.6% to 12.0%) reduction in the odds of AKI. The study had several limitations including the inability to determine with certainty if the administration of contrast preceded the diagnosis of AKI within any hospitalization (since AKI was determined solely based on administrative data) which placed the validity of its results into question. The more generalizable implication of the study itself seemed to be that 'sicker' patients are more liable to develop an AKI, with

or without the presence of contrast. A retrospective study with a total of 12,508 propensity score-matched patients reported that the incidence of AKI significantly increased with decreasing baseline eGFR (P<0.0001). However, this incidence was not significantly different between contrast material and non-contrast material groups in any eGFR subgroup, even in patients with eGFR of less than 30 mL/min/1.73 m^2 (14).

Intra-arterial contrast exposure is reported to be more nephrotoxic than intravenous use. Several studies have shown higher rates of AKI after coronary angiography (13%) compared to AKI rates with IV radiocontrast media exposure (5–6%), potentially due to higher concentrations of radiocontrast media delivered to the kidney and the shorter transit time to the kidneys (45,46). Patients undergoing primary PCI are at higher risk of CI-AKI compared with those undergoing elective interventions, though recently there has been data suggesting that risk of AKI with PCI may not be as pronounced as in prior studies. Caspi *et al.* used a prospective database to determine the causal association of contrast material exposure and the incidence of AKI following PCI using a control group of propensity score-matched patients with STEMI who were not exposed to contrast material (47). Among propensity score-matched patients, AKI rates were not significantly different with and without PCI (8.6% versus 10.9%, P=0.12). In the PCI cohort, independent predictors of AKI included age ≥70 years, insulin-treated diabetes mellitus, diuretic therapy, anterior infarction, baseline estimated glomerular filtration rate, and variables related to the presence of pump failure (higher Killip class, intra-aortic balloon pump use) and reduced left ventricular ejection fraction but not contrast material dose. They concluded the risk for AKI was similar among STEMI patients with and without contrast material exposure. This study was an observational one where some patients were recruited during a period in which both PCI and thrombolysis were acceptable reperfusion strategies. Despite propensity score analysis, treatment bias related to age, baseline renal function, infarct location, and hemodynamic status may have affected the decision to perform PCI, resulting in heterogeneity caused by AKI-predisposing comorbidities between contrast and non-contrast groups. Nonetheless this study raised the question of whether CI-AKI truly exists in the setting of coronary angiography, and determined it is unlikely that radiocontrast media is a primary pathogenic factor responsible for renal dysfunction.

Brown *et al.* examined the associations between PCI, AKI and CKD progression to study long-term consequences of PCI and development/progression of CKD (48). They classified cardiac catheterization-associated AKI (CCA-AKI) to represent a broad category of AKI that included contrast-induced nephropathy, as well as AKI attributable to atheroembolization, hypotension, and other causes associated with these procedures. A total of 48,810 patients were evaluated in three groups (PCI complicated by CCA-AKI, uncomplicated PCI, and controls), with controls well matched to PCI patients for age, diabetes mellitus, hypertension, heart failure, and baseline CKD stage. Of note, CCA-AKI developed in 13% of the PCI cohort, which was consistent with other reports, and PCI patients developing CCA-AKI were more likely to have urgent or emergent indications for intervention, exhibited greater temporal proximity to the diagnostic cardiac catheterization, and had angiographic evidence of more severe coronary disease. While this study did overcome the limitations of some prior studies including a large sample size, using laboratory based eGFR values rather than administrative diagnosis codes, and using a control group to help validate their findings, it was limited primarily by the definition used for CCA-AKI (which essentially included any cause of AKI occuring following PCI), thus rendering the study unable to truly classify how much of a role CI-AKI had in the overall development of AKIs.

A subgroup analysis of the PRESERVE (Prevention of Serious Adverse Effects Following Angiography) trial assessed IV sodium bicarbonate or IV sodium chloride and oral acetylcysteine or placebo for the prevention of CI-AKI and intermediate-term adverse outcomes (49). A subgroup analysis was conducted of the efficacy of these interventions in patients who underwent PCI during the study angiographic examination. There were no significant between-group differences in the rates of CI-AKI. In conclusion, among patients with CKD undergoing PCI, there was no benefit of IV sodium bicarbonate over IV sodium chloride or of acetylcysteine over placebo for the prevention of CI-AKI or intermediate-term adverse outcomes. The study was limited by the reduced sample size from the overall PRESERVE trial, exclusion of patients CKD V or more acutely sick (STEMI), and the study population was predominantly male, impacting its generalizability. While this study did monitor several other factors that are likely to influence CI-AKI (such as volume and type of contrast used), it failed to consider other potential causes of AKI (such as peri-PCI hypotension), thus raising the question once again regarding the true incidence of CI-AKI.

A recent study done examined data obtained from 323 consecutive patients with advanced renal dysfunction (eGFR <30 mL/min/1.73 m^2) to address the occurrence and prognostic influence of CIN in patients with advanced renal dysfunction (50). CI-AKI was observed in 31 patients (9.7%), and a comparison between patients with and without CIN showed no significant intergroup differences in the occurrence of all-cause death or the initiation of permanent dialysis. The authors concluded that the incidence of CI-AKI was not higher in Japanese patients with advanced renal dysfunction in routine clinical practice, and that CI-AKI did not show a significant prognostic influence.

Summary and conclusions

Contrast-induced AKI has become a topic of much debate in the practice of medicine. While a substantial amount of time and resources have been devoted to try and better define it or to disprove it, no study has so far succeeded in answering the question conclusively. In more recent years, there does seem to have been more of a trend of questioning the existence of CI-AKI as a true entity, with multiple studies failing to find any association between radiocontrast media exposure and renal injury. Several mechanisms have been proposed to explain the pathogenesis of CI-AKI, but it should be recalled that this data was derived from animal models. The diagnosis of CI-AKI, per its very definition, is based on the clinical presentation and time to development, and as such remains a diagnosis of exclusion. More recently, when AKI following contrast exposure cannot be ascribed to contrast exposure, the term post-contrast AKI has been labeled, emphasizing the temporal relationship between contrast exposure and AKI (19,51).

Several of the studies reviewed were comprehensive in their designs but neglected to account for other more commonly accepted causes of AKI that impacted the validity of their results. Other studies acknowledged other etiologies yet chose to group all AKIs under an umbrella term such as cardiac catheter-associated AKI, which did not help to clarify the incidence of CI-AKI (15). The occurrence of CI-AKI was likely overestimated in the past because of confounders for AKI. While none of the studies have managed to prove or disprove CI-AKI conclusively, they have built up several thought-provoking points regarding the subject. Patients with more severe illnesses are more predisposed to developing AKI independent of their risk of potential CI-AKI, and predictably, their overall prognosis is poor (12,13,18). This raises concern for potentially life-saving testing/interventions being deferred or suspended for patients deemed at risk for AKI out of fear of causing CI-AKI. Preventative measures to counter potential CI-AKI appear to be becoming the standard of care for several contrast-associated procedures, with questionable evidence as to whether the AKI that is being prevented is truly CI-AKI or another more common cause of AKI. Thus, labelling every AKI that follows a contrast study as CI-AKI without doing the due diligence of an appropriate workup would be considered a disservice to the patient.

The best way of settling the matter would be to design a randomized controlled trial of patients undergoing coronary angiography and/or PCI with and without CKD, while controlling for other risk factors and confounders. Each patient should have documented pre-procedure baseline renal function and urine studies (volume, sp. gravity, blood, protein levels), then have their perioperative vitals, cardiac status, blood loss recorded, followed by a post-operative tracking of daily serum creatinine for a minimum of 72 hours. The occurrence of an AKI should prompt an appropriate workup to rule out all other plausible etiologies before the determination of CI-AKI can be made. Since clinical assessment can be subjective, ideally it should be independently verified by two different physicians. Such a method may still not guarantee an absolute answer but should allow for a better determination of the incidence of CI-AKI than is available literature so far. Unfortunately, time, financial, and perhaps even ethical constraints would ensure that such an endeavor may be extremely challenging to arrange, and so a definitive answer on CI-AKI, and whether it really exists, may continue to elude clinicians.

Footnote

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