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

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ABSTRACT

The administration of iodinated contrast medium (CM) has immediate negative impact on multiple levels of the nephron, including vasoconstriction, an increase in apoptotic pathways and oxidative stress. Therefore, contrast-induced acute kidney injury (CI-AKI) remains an important cause of sudden impairment of renal function. Far from being just a transient phenomenon, CI-AKI has consistently been shown to be associated with adverse outcomes. The phenomenon of chronic kidney disease (CKD) following AKI might explain why this entity portends a poor prognosis in the long run. While it is generally acknowledged that in individuals with normal renal function, the risk of CI-AKI is negligible, pre-existing renal disease is its greatest independent risk factor. Although several recent publications have challenged the dogma of CI-AKI as a stand-alone disease entity, these trials, despite careful propensity matching, are hampered by their retrospective nature. In this article, we concede that there is always a trade-off and that administration of CM may be justified if its diagnostic value is believed to outweigh its associated risks. However, we reason that despite considerable progress in the field, the risk of CI-AKI is still high in the modern era and that CM-based imaging should be employed with great restraint in patients with CKD.

Keywords: acute renal failure, AKI, CI-AKI, chronic kidney disease, contrast media

INTRODUCTION

Among the various causes of sudden impairment of renal function, contrast-induced acute kidney injury (CI-AKI), previously referred to as contrast-induced nephropathy, stands alone as a common iatrogenic and therefore, at least theoretically, preventable condition. For decades, a substantial proportion of AKI has been attributed to exposure to iodinated contrast medium (CM); a strong correlation exists between CI-AKI and adverse short- and long-term sequelae, including cardiovascular complications, need for dialysis and death [1]. Accordingly, several authorities have issued formal recommendations addressing its management [2–4].

PROPOSED PATHOPHYSIOLOGY OF CM CYTOTOXICITY

Multiple lines of evidence clearly demonstrate that CM is cytotoxic *in vitro* [5]. The nature (ionic strength, osmolality, viscosity) and volume of the contrast agent, as well as patient-related factors, may amount to clinically relevant kidney injury *in vivo*. The underlying pathophysiology, although not yet fully elucidated, cogently shows that the administration of contrast has immediate impact on multiple levels of the nephron; however, the renal tubule, as the metabolically most active component of the nephron, is particularly susceptible to such insults [6].

CM is fully eliminated via the kidney and not re-absorbed, leading to a change in tubulodynamics [7]; notably, the excretion half-life of contrast dye is considerably prolonged in chronic kidney disease (CKD), resulting in increased nephrotoxic exposure [8]. Damage attributable to direct cytotoxicity eventually leads to apoptosis, including a marked increase in caspase-3 and -9 activities, accompanied by an increased expression of pro-apoptotic members of the Bcl2 family [9]. This concept has been challenged recently in a murine model, highlighting that CM was not able to induce apoptosis of renal tubular cells [10]. After exposure to iodixanol, an iso-osmolar contrast agent (IOCM), vasoconstriction of vasa recta has been implicated in the occurrence of CI-AKI accompanied in part with an increase of vasoconstrictive cytokines (i.e. endothelin-1 and a medullary increase of endothelin converting enzyme-1), which was further aggravated by angiotensin II [7, 11, 12]. In addition, an imbalance of nitric oxide (NO) and reactive oxygen species (ROS) has been proposed. While iodixanol was capable of reducing NO bioavailability by >82% [11], the generation of ROS as a consequence of a decline in medullary blood flow and the increase in tubular transport activity may exert both vascular and tubular injury [13]. These effects further involve stress-related pathways, which are most prominently observed within outer medullary tubular cells undergoing the most extensive damage [7]. Taken together, renal vasoconstriction, an increase in apoptotic pathways and oxidative stress appear to be the main mechanisms underlying CI-AKI.

Definition and impact of AKI

CI-AKI is defined as 25% relative or a 0.5 mg/dL absolute increase in serum creatinine (SCr) within 72 h of contrast exposure, in the absence of an alternative explanation [4]. How might such a subtle (and usually fleeting) change in renal function trigger the purported far-reaching effects? Firstly, SCr alone is a notoriously insensitive indicator of kidney function. Secondly, small increments in SCr have been shown convincingly to adversely affect patients' outcomes [6]. Thirdly, during the past decade, the phenomenon of CKD following AKI (the so-called 'AKI-to-CKD continuum') has gained attention and its underlying pathophysiology could explain why CI-AKI portends a poor prognosis in the long term. In brief, AKI as a localized damage triggers a systemic inflammatory response; ensuing maladaptive repair, characterized by vascular dropout, tubular loss and interstitial collagen deposition, finally results in accelerated kidney ageing [14].

IMPAIRED RENAL FUNCTION AS RISK FACTOR FOR DEVELOPMENT OF CI-AKI

Based on individual risk profiles, the incidence of CI-AKI varies from 2% to 50% [15]. Independent predictors of CI-AKI encompass higher age, diabetes and heart failure [1]. By definition, patients with CKD carry a key risk factor for CI-AKI, namely baseline renal impairment [16]. It has been estimated that a third of all AKI episodes occur in individuals with pre-existing CKD [17]. Moreover, other risk factors such as age and diabetes gain in relevance when renal function is chronically impaired; in patients who undergo coronary angiography (CA), these components frequently coexist. A recent *Lancet* article only considers individuals with an estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m^2 as truly having low risk of CI-AKI [18]; accordingly, CKD Stage 3 onwards is widely accepted to carry clinically meaningful risk [3].

RISK OF CI-AKI IS STILL HIGH IN THE MODERN ERA

Two landmark papers illustrate that contemporary contrast agents still confer a formidable renal risk in patients with underlying CKD. The POSEIDON (Prevention of Contrast Renal Injury with Different Hydration Strategies) trial ($n = 396$; mean eGFR 48 mL/min/1.73 m^2) reported an overall incidence of CI-AKI of 11.4%; notably, these patients had a higher rate of all-cause mortality and myocardial infarction at 6 months [19]. Likewise, the PRESERVE (Prevention of Serious Adverse Events following Angiography) study ($n = 4993$; median eGFR 50.2 mL/min/1.73 m^2) reported an incidence of CI-AKI of almost 10% and the primary endpoint (a composite of death, need for dialysis or persistent creatinine increase at 90 days) occurred in almost 5% across all groups [20]. Overall, these results imply that in the era of modern CM, CI-AKI remains more than just a 'creatinopathy'. Moreover, in a pre-specified substudy of the Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox (MATRIX) trial, assessing the incidence of AKI in patients with acute coronary syndrome undergoing CA, the primary endpoint occurred in 15.4% with radial versus 17.4% with femoral access, further strengthening the importance of contrast agents as nephrotoxic culprit [21].

We are well aware of the ongoing debate that the risk of CM may be lower than widely perceived. Several recent publications have challenged the dogma of CI-AKI as a stand-alone disease entity, arguing that random changes in serum creatinine ('background noise') can result in AKI misclassification, irrespective of CM being present [22]. This discussion was fuelled by a recent observational study from a large national database concluding that the risk of CI-AKI may be overestimated [23]. However, the 'big data approach' and the observational nature of these reports remain important limitations [22].

Osmolality is a key determinant of the safety of radiocontrast. When compared with low-osmolar CM (LOCM), the newer class of IOCM exhibited a smaller risk for kidney injury across various trials, but a recent meta-analysis questioned the clinical relevance of this difference [24]. However, one particular LOCM agent, iohexol, may be associated with increased nephrotoxicity compared with other CM of this category and should be avoided in at-risk individuals [25]. Otherwise, current guidelines do not make recommendations about selection between LOCM and IOCM [1].

The application of intra-arterial CM has usually been associated with a higher incidence of CI-AKI when compared with CM given in the venous system. This may be attributed to renal atheroemboli and not to CM itself ('competitor strike') as well as different degrees of dilution between intravenous and intra-arterial application. Interestingly, McDonald *et al.* recently reported a similar risk of AKI after intra-arterial and intravenous administration of CM (9.9% versus 11%) in a large cohort of patients that received both routes of administration. From this, we would deduce that even intravenous CM poses no trivial risk for nephrotoxicity [26].

CAN CM BE APPLIED IN ADVANCED CKD?

We concede that it is difficult to prove cause and effect in the field of CI-AKI and that a '*post hoc*, *ergo propter hoc*' reasoning has been in place for too long. Likewise, we do not claim that the use of iodinated radiocontrast should be considered an absolute contraindication even in patients with advanced kidney impairment. For instance, few would argue that a CKD patient with an ST-elevation myocardial infarction should not undergo urgent CA. Indeed, concerns have been voiced that patients with CKD are frequently denied contrast-enhanced procedures because of exaggerated fears about nephrotoxicity irrespective of the diagnostic and prognostic benefits they might impart. However, in another true emergency, namely pulmonary embolism, strict adherence to clinical decision rules in conjunction with specific markers (D-dimer) can considerably reduce the number of computed tomography scans ordered, without negative impact on patients' outcomes [27].

Along similar lines, the common practice of performing pre-emptive CA in asymptomatic transplant candidates stands to prove that any benefits gained by this approach outweigh the associated risk; available data are limited to small, observational studies [28, 29]. Again, the same comorbidities that trigger

angiography (age, diabetes, heart failure) render these individuals highly vulnerable for CI-AKI.

It should be noted that diagnostic alternatives exist for various clinical scenarios—admittedly all with their own inherent limitations—such as ventilation/perfusion-scanning, unenhanced magnetic resonance angiography and contrast-enhanced ultrasound, using alternative CM. Newer, non-iodine-based compounds are in the pipeline; their renal safety profile remains to be established.

Lastly, no single adjunctive pharmaceutical intervention—with the possible exception of volume expansion—has been shown to effectively prevent or treat CI-AKI. The adage goes that prevention is better than cure. Therefore, one can argue that the most effective measure to prevent CI-AKI is to withhold contrast if the circumstances permit.

CONCLUSION

Despite much progress in the field of CI-AKI, it remains a common complication and is, either as a mediator or a marker, linked to adverse outcomes. Its risk is real, and patients with CKD are particularly susceptible. In view of our long-term clinical experience with this entity, plausible underlying pathophysiology and recent data regarding 'chronic on acute' kidney disease, we believe that the burden of proof of the safety of CM in CKD must lie with the proponents of its more liberal usage. Nevertheless, for the sake of a dialectic discussion, may we be allowed a conciliatory concluding line: as risk–benefit analyses have become an integral part in medical decision-making, we will have to stop thinking in black and white terms. Choosing the most appropriate diagnostic study should always involve estimating the pretest probability of significant underlying disease, the diagnostic utility of various available imaging modalities and the risks inherent with each, as well as any therapeutic consequences. If, therefore, after careful deliberation, a radiocontrast-based investigation is deemed essential, a multimodal approach aimed at CI-AKI prevention should be employed and early (ideally pre-procedural) liaison with nephrologists should be self-evident.

CONFLICT OF INTEREST STATEMENT

None declared.

(See related article by Ewing and Eidt. Con: Contrast-induced nephropathy—should we try to avoid contrast media in patients with chronic kidney disease? *Nephrol Dial Transplant* 2018; 33: 1320–1322)

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