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EDITORIAL

Contrast-associated acute kidney injury is a myth: No

Steven D. Weisbord[1,2*] and Damien du Cheryon[3]

Introduction

The intravascular administration of iodinated contrast media has been a recognized etiology of acute kidney injury (AKI) for decades [1]. Recent studies have questioned the causal association of iodinated contrast administration with acute impairment in kidney function [2–7]. Review of specific lines of past scientific inquiry on contrast administration and AKI and critical analysis of recent research questioning this association demonstrates that contrast-associated AKI (CA-AKI) is not a myth.

Discussion

The effects of contrast on the kidney

Past research on the physiologic effects of intravascular contrast in the kidney supports the nephrotoxicity of iodinated contrast (Fig. 1). In some animal models, the intravascular administration of iodinated contrast results in decreased renal blood flow to and a reduction in the partial pressure of oxygen of the outer renal medulla, a segment of the kidney that is particularly vulnerable to perturbations in oxygen supply [8, 9]. This adverse hemodynamic effect of contrast was also observed in studies of healthy human subjects using blood oxygen level-dependent MRI, in which the intravascular administration of iodinated contrast reduced renal medullary blood flow. Contrast administration in animals has also been shown to increase the generation of oxygen free radicals, an effect that is associated with a decrease in glomerular filtration [8]. Finally, in vitro studies demonstrate that iodinated contrast has adverse effects on mitochondrial enzyme activity and membrane function and contributes to apoptosis of renal tubular epithelial cells [10, 11]. Although findings in animal models do not necessarily translate to humans and the aforementioned studies in animals have certain methodologic limitations, these and other studies provide a pathophysiologic basis for the nephrotoxicity of iodinated contrast.

Volume and type of contrast agent

Several studies have identified an association of a higher volume of iodinated contrast with increased risk of AKI [12]. While such analyses are confounded by the recognition that sicker patients with more complex clinical presentations (who are hence at higher baseline risk for AKI) may undergo procedures that require higher volumes of contrast, this 'dose-response' relationship between contrast volume and risk of renal injury supports the nephrotoxic potential of these agents. Furthermore, past studies that compared the effects of different contrast agents support their causal association with AKI [13]. The initial contrast media used in clinical practice were 'high osmolal' with osmolalities several fold greater than blood (i.e., 1500–2000 mOsm/kg). Following the introduction of 'low-osmolal' contrast media (osmolality ~ 600–850 mOsm/kg), clinical trials and meta-analyses demonstrated lower risk for CA-AKI with these agents compared with 'high-osmolal' media [14]. A differential risk of AKI was also observed in certain more recent studies that demonstrated lower rates of CA-AKI following procedures that used iso-osmolal iodixanol compared with certain 'low-osmolal' agents [15]. While differences between iodixanol and 'low-osmolal' contrast regarding the risk for AKI were not shown in all prior trials, one would not expect to see any differences in the incidence of renal injury with these agents if they had no adverse effects on the kidneys.

*Correspondence: weisbordsd@upmc.edu
[1] Renal Section and Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare System, Mailstop 111F-U, University Drive, Pittsburgh, PA 15240, USA
Full author information is available at the end of the article

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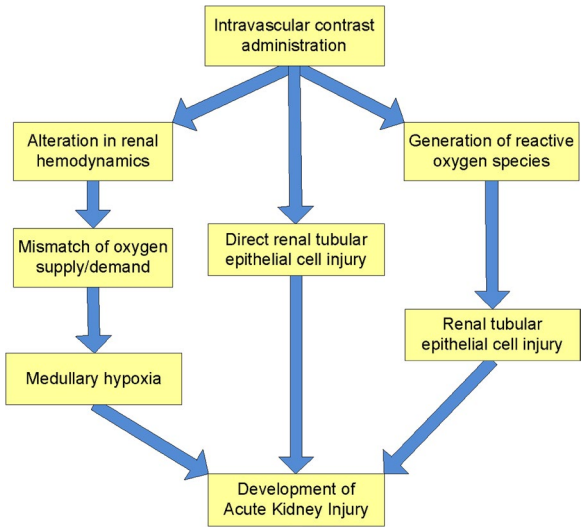

Fig. 1 Pathophysiology of acute kidney injury following intravascular contrast administration

Recent studies questioning the existence of CA-AKI

Notwithstanding past research that documented the pathophysiologic effects of iodinated contrast on the kidneys and differential risk of AKI based on volume and type of contrast agent, multiple recent studies have questioned the existence of CA-AKI [2–6]. A meta-analysis by McDonald and colleagues that included 13 studies with a total of 25,950 patients demonstrated that the risk of AKI following procedures with intravascular contrast administration was similar to the risk following procedures that did not utilize contrast (relative risk, 0.79; 95% CI, 0.62–1.02) [3]. The authors also reported no differences in the need for dialysis or death based on the receipt of contrast. More recently, Wilhelm-Leen et al. compared the incidence of AKI in a large cohort of hospitalized patients who did and did not undergo contrast-enhanced procedures [7]. In adjusted analyses, the incidence of AKI was 5.1% in patients who received contrast compared with 5.6% in those who did not (adjusted odds ratio, 0.93; 95% CI, 0.88–0.97).

While these and several other studies form the basis for the current hypothesis that CA-AKI does not exist, careful inspection of these studies demonstrates certain methodologic limitations that raise questions about the findings. First, all of these studies were retrospective observational analyses that relied on data that had been collected as part of routine clinical care. As such, the results were based solely on those patients in whom renal function was assessed prior to and following radiographic procedures. Furthermore, differential assessment of kidney function, regardless of reason, could not be fully accounted for in the analyses. Second, the use of preventive care to mitigate the risk of CA-AKI could not be fully evaluated. For example, demonstrating that the incidence of AKI is similar in patients who receive aggressive intravascular volume expansion before receiving iodinated contrast compared with patients who undergo non-contrast enhanced procedures would not establish that intravascular contrast is not nephrotoxic. Finally and most importantly, these studies could not fully account for factors that influenced providers' decisions regarding the use of intravascular contrast. Patients at higher baseline risk of AKI were almost certainly less likely to receive intravascular contrast than patients at low baseline risk. No degree of statistical adjustment or propensity score matching can fully account for all potential confounders or eliminate the effect of indication bias. In fact, the likelihood that there were substantial differences in baseline risks for AKI between patients who did and did not receive contrast is borne out in the findings of some of these studies that demonstrated statistically significantly lower rates of CA-AKI among patients who received contrast compared with patients who did not [4, 7]. Unless one believes that intravascular iodinated contrast is nephroprotective, this observation highlights the likelihood of confounding by indication in such studies.

Conclusion

In summary, prior research has elucidated pathophysiologic effects of iodinated contrast on the kidneys in animal models and humans, while studies documenting associations of volume and osmolality of contrast media with risk for renal injury support their nephrotoxic potential. Recent studies questioning the existence of CA-AKI have important methodologic limitations that confound interpretation of their findings. While secular trends including the use of lower volumes of less nephrotoxic contrast along with the widespread use of preventive care including intravascular volume expansion have likely contributed to decreased rates of CA-AKI and rendered severe renal injury a relatively rare complication of contrast administration alone, these factors have not eliminated the existence of this iatrogenic condition. Continued vigilance and appropriation of evidence-based preventive care in the highest risk patients remains essential.

Author details

[1] Renal Section and Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare System, Mailstop 111F-U, University Drive, Pittsburgh, PA 15240, USA. [2] Renal-Electrolyte Division, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA. [3] CHU de Caen, Service de Réanimation Medicale, Caen, France.

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Conflicts of interest

The authors declare that they have no competing interests. The opinions expressed in this article are those of the authors and do not necessarily represent those of the U.S. Department of Veterans Affairs.

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EDITORIAL

Contrast-associated acute kidney injury is a myth: Yes

Stephan Ehrmann[1,2,3*], Doron Aronson[4,5] and Jeremiah S. Hinson[6]

Introduction

Contrast medium (CM) administration is widely cited as a leading cause of hospital-acquired acute kidney injury (AKI) [1]. Concern over precipitation of AKI by CM is pervasive, and has influenced clinical decision-making related to diagnostic imaging and therapeutic interventions for more than half a century. So-called contrast-induced AKI (CI-AKI) is defined as an acute impairment in renal function occurring within 3 days of CM administration *that is not attributable to any other etiology* [1, 2]. Yet, nearly all studies establishing CI-AKI as a clinical entity were performed in the absence of control populations not exposed to CM. These studies assumed causality from association, and considered all cases of AKI in CM-exposed patients as CI-AKI, even when alternative explanations were obvious (Fig. 1) [3–5]. A growing body of evidence, derived from studies that include adequate control populations and discussed in more detail below, now suggests that risk for AKI attributable to CM administration is modest at most. Yet, outsized fear of CI-AKI persists.

Clinical importance

The distinction between a causal and associative relationship between CM and AKI is not purely academic. The prevailing belief that CM plays a central role in AKI has had major impacts over several decades, including promotion of potentially suboptimal clinical care at the patient level and subversion of a research agenda at the scientific level. Withholding CM on the basis of overestimated risk deprives individual patients of diagnostic studies and therapeutic interventions, many of which convey substantial proven benefit [6, 7]. There are scenarios in which CM administration is unavoidable, however, and the perceived risk of CM administration associated with such scenarios has driven intense interest in preventive measures for CI-AKI. Indeed, an entire field of investigation aimed at their identification and evaluation has been established. An enormous amount of funding has been allocated to this line of research and a very large number of patients have been exposed to experimental interventions including *N*-acetylcysteine, sodium bicarbonate, fluid loading, statins, vitamin C, vasoactive medications, theophylline, preconditioning ischemia, and renal replacement therapy—none of which are devoid of side effects [8]. The preponderance of negative trials testing similar preventive strategies for CI-AKI is in itself a strong argument against a causative relationship between CM and AKI, and even raises potential ethical concerns for enrollment of patients in such studies. Interestingly, all three authors of this editorial, as initial believers in CI-AKI, planned or initiated interventional trials aimed at its prevention in their respective fields of emergency medicine, critical care, and cardiology. In doing so, each abandoned their efforts after independently concluding, in the light of the available literature, that the role of CM in AKI has been vastly overestimated.

Intravenous contrast media and acute kidney injury in the general population

Studies performed in unselected populations with controls do not support a meaningful role for intravenous CM in causing AKI. Meta-analysis of 13 studies in which incidence of AKI was directly compared between patients who were and were not exposed to CM failed to demonstrate any increased risk of AKI, dialysis, or death associated with CM [9]. This is supported by a recent nationwide analysis of administrative data for almost 6 million patients in the USA, where rates of AKI were

*Correspondence: stephanehrmann@gmail.com
[1] Médecine Intensive Réanimation, CHRU de Tours, Tours, France
Full author information is available at the end of the article

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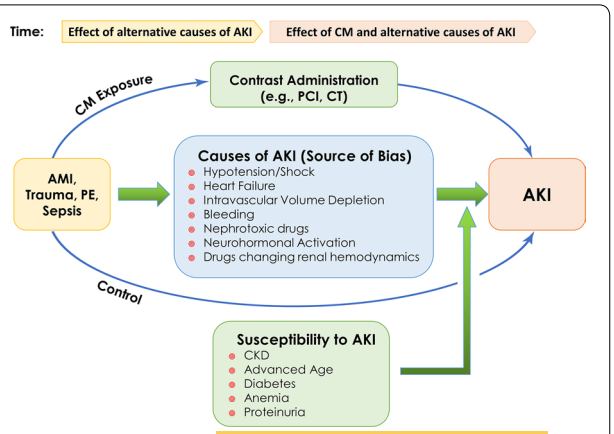

Fig. 1 Diagram showing the importance of negative controls in evaluating the causal relationship between contrast media (CM) exposure and acute kidney injury (AKI). Regardless of the decision to use CM, acute illness (acute myocardial infraction, sepsis, trauma, etc.) produces a set of alternative conditions that can independently initiate the process of AKI prior to, during, and after the administration of CM. Note that the potential bias introduced by other causes of AKI increases with increasing severity of the acute illness. The essential purpose of the negative control group is to reproduce a condition that does not include the hypothesized causal mechanism but is very likely to involve the same sources of bias that are often present in the original association. If contaminants (source of bias) were responsible for the effect of the CM, they should exert their effect even when CM is not present. A control group allows us to estimate the true effect of CM exposure given the background of multiple confounders. In controlled studies, the outcome (AKI) is encountered without exposure to CM, demonstrating the existence of a confounding bias. AMI acute myocardial infarction, PE pulmonary embolism, PCI percutaneous coronary intervention, CT computed tomography, AKI acute kidney injury, CM contrast media, CKD chronic kidney disease

nearly identical in patients who did and did not receive CM [10]. Direct comparison of populations, as performed in these studies, is confounded by selection bias associated with the decision to administer or withhold CM. Several subsequent studies have utilized propensity matching analysis to minimize this bias. None of these studies identified an independent association between intravenous CM administration and risk for AKI, dialysis, or death in the general population [11–13]. While one group did report increased risk of AKI associated with CM administration in the less than 5% of patients with an estimated glomerular filtration rate below 30 mL/min/1.73 m^2, two others did not [11–13].

Contrast media and acute kidney injury in the critically ill

Critically ill patients have long been considered a population at particularly elevated risk of CI-AKI [14]. A recent systematic review revealed that this belief has been driven by a large body of uncontrolled data [15]. Meta-analysis of three propensity-matched controlled studies showed a lack of significant difference in AKI incidence among 560 critically ill patients who were exposed or unexposed to CM [15]. Those data were reinforced by a large monocentric database analysis showing a lack of significant association between CM and AKI, renal replacement therapy, and mortality among 6877 propensity-matched intensive care unit patients [16]. These findings have important clinical implications, as the utility of CM for diagnosis and treatment of immediately life-threatening conditions may be even greater among critically ill patients than in the general population.

Contrast media and acute kidney injury in patients undergoing percutaneous intervention

The reported incidence of CI-AKI following percutaneous intervention (PCI) ranges from 1–2% in patients undergoing elective PCI to 10–20% in patients undergoing PCI for ST-elevation myocardial infarction (STEMI) [1, 3, 4, 7]. While attributed to CM exposure, the marked increase in AKI rates in these patients more likely results from associated conditions including hypotension, hemodynamic instability/cardiogenic shock, acute heart failure, hemorrhage, and initiation of medications that alter renal hemodynamics (Fig. 1). Indeed, multiple retrospective controlled studies in patients undergoing PCI were unable to show a meaningful adverse effect of CM exposure [6, 7, 10]. Further, a study performed in a large inpatient sample that controlled for comorbidity and acuity of illness found that patients with acute coronary syndromes (n = 1,251,812) who received CM experienced an unexpectedly lower rate of AKI as compared to patients who were not exposed to contrast (6.4% versus 17.4%) [10]. Finally, a propensity-matched cohort study of patients with non-STEMI reported one additional episode of AKI for every 62 participants treated with an early invasive approach instead of a conservative approach, with similar risks of dialysis or long-term risk of end-stage renal disease, but better long-term survival with the invasive approach [6] and in a propensity-matched cohort study of patients with STEMI, the risk of AKI was similar with and without CM exposure [7].

Conclusion

Mythology and science share a common purpose: to provide meaning to and understanding of phenomena that are readily observed but not easily explained. The two disciplines diverge dramatically in process, however, with the prior relying on imagination and conjecture and the latter on a rigorous method that includes observation followed by hypothesis formulation, testing through structured experimentation, and finally rejection or acceptance. In keeping with this, and the data discussed above, we support the clause under debate:

contrast-induced acute kidney injury is a myth. The concept of CI-AKI arose from observation and assumed causality, and despite a lack of rigorous hypothesis testing, has driven clinical practice for more than five decades. While a randomized controlled trial has not been conducted, there is now substantial evidence suggesting that CM contributes minimally, if at all, to the development of AKI [6, 7, 9, 11, 13, 15–17]. Despite the existence of such evidence, a pervasive preoccupation with what should be referred to as contrast-*associated* AKI (CA-AKI) persists in clinical practice, medical texts, and even among clinical researchers. There are many well-established risk factors for AKI (Fig. 1), many of which have clear causal relationships with AKI and are readily modifiable, yet are often ignored as episodes of AKI are attributed to CM. Disproportionate focus on CM also results in misappropriation of critical human and monetary capital that could be more effectively harnessed to reduce AKI-associated harms.

Author details
[1] Médecine Intensive Réanimation, CHRU de Tours, Tours, France. [2] Faculté de médecine, Université François Rabelais, Tours, France. [3] CRICS-Triggersep Network, Tours, France. [4] Department of Cardiology, Rambam Medical Center, Haifa, Israel. [5] Ruth and Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel. [6] Department of Emergency Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

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EDITORIAL

Contrast-associated acute kidney injury is a myth: We are not sure

Kianoush Kashani[1,2*], Adeera Levin[3] and Miet Schetz[4]

Introduction

Contrast-induced nephropathy, recently renamed "contrast-associated acute kidney injury (CA-AKI)" or "post-contrast AKI (PC-AKI)" is considered an iatrogenic cause of AKI with adverse short- and long-term outcomes [1]. Over the past years, the evidence for a causal association between contrast and AKI has been challenged. We use the Bradford–Hill criteria to re-evaluate this relationship.

Discussion

Strength of association

The reported incidence of CA-AKI is variable (1–30%), and also a wide range of risk ratios for mortality after CA-AKI (range 0.79–9.52) have been described [1]. This variability suggests that there may be a weaker association between contrast exposure and AKI per se; this, in turn, could be highly influenced by other risk factors for AKI. The heterogeneity among study designs and CA-AKI definitions also contributes to this variability.

Consistency

In the absence of randomized controlled trials, the evidence for CA-AKI must rely on observational data. Recent reports debate the association between contrast exposure and AKI in different settings (Table 1). A meta-analysis of studies comparing patients with and without intravenous (IV) contrast imaging described no increased incidence of AKI, dialysis, or death with contrast [2]. To reduce selection bias, several subsequent studies have used propensity score matching. Most studies found no difference in the incidence of AKI among matched patients. Subgroup analyses based on baseline kidney function also did not show any differences, except for the study by Davenport that found a higher AKI incidence after contrast in advanced chronic kidney disease (CKD) [3]. McDonald found a greater need for dialysis in ICU patients with pre-CT eGFR $\leq$ 45 ml/l/BSA (6.7% vs 2.5%; OR 2.72 (1.44–6.46), however, without impact on the AKI creatinine criterion [4].

Other studies, including some with intra-arterial contrast, demonstrate that AKI incidence is the same in the matched patients, regardless of exposure to contrast. Caspi et al. showed no difference in the AKI incidence between primary PCI (contrast group) and fibrinolysis or no reperfusion (no contrast group) in patients with ST-segment elevation myocardial infarction [12]. Wilhelm-Leen et al. found a lower AKI incidence in patients receiving "any contrast." However, the diagnosis of both AKI and contrast administration was based on ICD-9 codes, no temporal relation was assessed, and risk factor adjustment was limited [13]. It is interesting that in one study, the Mehran risk score for CA-AKI had the same predictive power in patients with and without contrast [11, 14].

Some caution in the interpretation of these case–control studies is warranted because even propensity score matching cannot correct for unmeasured or unknown confounders. In addition, most of these studies do not provide data on prophylactic measures (including prehydration) that might be different in cases and controls.

Temporality

There is a consistent temporal relationship described in all studies (observed vasoconstriction of afferent arterioles after exposure to contrast media in animal models and AKI after exposure to contrast in clinical studies); however, the current literature suffers from selection bias and suboptimal trial design. For example, in none of the

*Correspondence: kashani.kianoush@mayo.edu
[1] Division of Pulmonary and Critical Care Medicine, Department of Medicine, Mayo Clinic, Rochester, MN, USA
Full author information is available at the end of the article

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Table 1 Studies to evaluate the impact of contrast media on the AKI incidence

	Setting	Sample size	Baseline kidney function	AKI + contrast (%) − contrast (%)	OR (adjusted[b])	Comments
McDonald et al. [2]	MA controlled studies	13 studies 25,950 patients		6.4 6.5	0.79 (0.62–1.02)	Similar results in subgroups with diabetes, renal insufficiency, type of contrast
McDonald[a] et al. [5]	CT	21,371	Scr < 1.5 mg	3 3	0.93 (0.76–1.13)	Single-center retrospective Propensity score matching (also in subgroups)
			Scr 1.5–2.0	9 9	0.97 (0.81–1.16)	
			Scr > 2	10 11	0.91 (0.66–1.24)	
Davenport[a] et al. [3]	CT	17,652	All patients	6.9 7.1		Single-center retrospective Propensity score matching Adjusted analysis in subgroups
		13,967	CKD I + II	5.4 5.5	1.00 (0.86–1.16	
		2480	CKD IIIa	10.5 10.8	1.06 (0.82–1.38)	
		1089	CKD IIIb	16.7 14.2	1.40 (1.00–1.97)	
		116	CKD IV–V	36.4 19.4	2.96 (1.22–7.17)[‡]	
Ehrmann[a] et al. [6]	ICU	292	All patients (CKD 7%)	5.5 5.5	1.57 (0.69–3.53)	Single-center retrospective Propensity score matching
McDonald[a] et al. [7]	CKD + CT	2440	CKD III	10 15	0.65 (0.41–0.89)	Single-center retrospective Propensity score matched
			CKD IV–V	21 20	1.14 (0.78–1.50)	
Hemmett et al. [8]	CT	370		10.7 9.1	Adjusted *p* 0.11	Multicenter retrospective Adjusted for age, gender, and baseline eGFR
Ehrmann[a] et al. [9]	MA controlled ICU studies	560			0.95 (0.45–1.62)	
McDonald[a] et al. [4]	ICU + CT	2446	eGFR > 45	14 14	1.00 (0.79–1.26)	Single-center retrospective Propensity score matched
		570	eGFR ≤ 45	29 25	1.28 (0.89–1.85)	
Hinson et al. [10]	ED + CT		Scr > 4 mg/dl		1.00 (0.99–1.01)	Single-center retrospective Propensity score matching (similar results in eGFR subgroups)
	CT + Contrast	7201	Excluded	6.8		
	CT− Contrast	5499		8.9		
	No CT	5234		8.1		
Petek et al. [11]	Cardiac arrest survivors (48 h)	199			0.72 (0.32–1.61)	Single-center retrospective Adjusted for Mehran score
	+ Contrast	94		12.8		
	− Contrast	105		17.1		

Table 1 continued

	Setting	Sample size	Baseline kidney function	AKI + contrast (%) − contrast (%)	OR (adjusted[b])	Comments
Caspi[a] et al. [12]	STEMI	1862			0.77 (0.56–1.06)	Single-center retrospective Propensity score matched (no-contrast patients treated earlier in study period)
	+ PCI	931		8.6		
	− PCI	931		10.9		
Wilhelm-Leen et al. [13]	Adult hospitalized	29,940,445	NR		0.93 (0.88–0.97)[‡]	AKI based on administrative data Adjusted for comorbidity and MV
	+ Any contrast	1,667,694		5.5		
	− Any contrast	28,272,751		5.6		

Scr serum creatinine, *CT* computed tomography, *IV* intravenous, *IA* intra-arterial, *STEMI* ST-elevation myocardial infarction, *PCI* percutaneous coronary intervention, *NR* not reported, *MV* mechanical ventilation

‡ Statistically significant

[a] Propensity score matched study. If propensity score matching is used only the matched cohort is shown

[b] If reported the adjusted OR is given

previous studies investigators attempted to identify subclinical AKI prior to enrollment; therefore, it may have resulted in the inclusion of the patients who had tubular injuries before contrast exposure.

Dose–response relationship

The contrast dose is considered a significant risk factor of CA-AKI both in experimental settings and in humans undergoing cardiac angiography. Contrast dose is included in CA-AKI risk scores [7] but may be confounded by indication. For example, patients with diabetes and chronic kidney disease have a higher risk for CA-AKI but frequently also have multi-vessel disease, which requires a higher dose of contrast during coronary angiography. Furthermore, few studies report the severity of AKI, thus limiting documentation of a dose–response relationship.

Plausibility

The primary proposed mechanisms of CA-AKI are direct cellular toxicity and vasoconstriction. Studies that focus on the use of cytoprotective and vasodilatory medications for CA-AKI prevention have yielded inconsistent results [5, 15–17]. Such variability in the documentation of benefit of interventions that address the underlying mechanisms may indicate their inefficacies in CA-AKI prevention and also could reflect the limited clinical importance of contrast toxicity. In addition, even if these interventions show benefit, it may not necessarily be related to prevention of contrast toxicity. For example, a recent study suggests that the protective effect of statins in patients with acute coronary syndrome undergoing coronary intervention is only seen in patients with high CRP, a parameter of inflammation that by itself is a risk factor for AKI amenable by statins [18]. Also, the improvement of kidney function with hydration is not specific to CA-AKI [19].

Coherence

There has been some coherency between the basic research findings with clinical observations. In cell culture models with renal endothelial and epithelial cells, contrast media lead to cell damage [15–17]. However, in animal models, pre-exposure to other kidney insults (dehydration, nephrotoxins, etc.) is necessary before CA-AKI development. This is coherent with the clinical scenarios where AKI is rarely seen when contrast is the only exposure and patients need multiple insults before CA-AKI develops.

Experimental data

Although several studies demonstrate that intravenous hydration combined with cytoprotective drugs can potentially prevent CA-AKI, this is not a consistent finding. Some of the interventions may directly impact the serum creatinine concentration independent of the GFR (decreased production, dilution, osmolar load-induced augmented renal clearance). Hence, observed CA-AKI prevention by these interventions could be solely due to biases of the diagnostic test (serum creatinine).

Alternate explanations

Studies that reported a relationship between contrast exposure and AKI rarely consider alternative causes of AKI. Since most patients receiving contrast have other AKI risk factors or kidney insults, and there is no CA-AKI-specific test or biomarker to exclude alternative

causes of AKI, attributing the causal relationship that is reported in the CA-AKI literature is challenging.

Specificity

CA-AKI definition has two distinct components: "0.3 mg/dl or 50% increase in creatinine within 24–72 h after contrast" and "cannot be attributed to other causes"; the latter element is often neglected, or difficult to determine on the basis of study design/data limitations. Besides the traditional risk factors including CKD, diabetes, age, hypertension, congestive heart failure, high osmolality, or high dose contrast, many patients who receive contrast have other AKI risk factors including dehydration, hypovolemia, low cardiac output, inflammation, sepsis, nephrotoxins, atheroembolism, etc. Results of current literature may be biased on the basis of the lack of specificity of defining CA-AKI in administrative and other datasets.

Conclusion

Applying the Bradford–Hill criteria to evaluate the causality relationship between contrast and AKI reveals significant uncertainty that is also reflected in the ongoing debate in contemporary literature. Considering the available data, we must conclude that the risk of contrast nephropathy is probably not zero but much lower than previously estimated and mainly confined to patients with multiple risk factors. Quantifying the magnitude of the CA-AKI risk requires more sophisticated studies and analyses than currently exist. In clinical practice, decisions regarding contrast administration should weigh individual risk factors with the diagnostic yield and therapeutic consequences of the imaging procedure. Future research should test appropriate implementation of individualized preventative measures in high-risk individuals.

Author details

[1] Division of Pulmonary and Critical Care Medicine, Department of Medicine, Mayo Clinic, Rochester, MN, USA. [2] Division of Nephrology and Hypertension, Department of Medicine, Mayo Clinic, Rochester, MN, USA. [3] Division of Nephrology, University of British Columbia, Vancouver, BC, Canada. [4] Clinical Department and Laboratory of Intensive Care Medicine, Division of Cellular and Molecular Medicine, KU Leuven University, Herestraat 49, 3000 Louvain, Belgium.

Compliance with ethical standards

Conflicts of interest

None of the authors has any conflict of interest regarding this manuscript. Kianoush Kashani serves on the advisory board of the "Phase IV Placebo-Controlled Non-Inferiority Randomized Study of the Effect of Intravenous Iso-Osmolar Iodinated Contrast Material Iodixanol (Visipaque™ Injection 320 mg-I/ml) On Renal Function in Post- Endovascular Abdominal Aortic Aneurysm Repair Adults With Stage III or Stage IV Chronic Kidney Disease" study sponsored by GE.

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