*Intensive Care Med (2018) 44:110–114*
https://doi.org/10.1007/s00134-017-4970-2

EDITORIAL

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

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## 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 pre-hydration) 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

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For contrasting viewpoints, please go to https://doi.org/10.1007/s00134-017-4950-6 and https://doi.org/10.1007/s00134-017-5015-6.

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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<br>+ contrast (%)<br>− contrast (%) | OR (adjusted[b]) | Comments |
|---|---|---|---|---|---|---|
| McDonald et al. [2] | MA controlled studies | 13 studies<br>25,950 patients | | 6.4<br>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<br>3 | 0.93 (0.76–1.13) | Single-center retrospective<br>Propensity score matching (also in subgroups) |
| | | | Scr 1.5–2.0 | 9<br>9 | 0.97 (0.81–1.16) | |
| | | | Scr > 2 | 10<br>11 | 0.91 (0.66–1.24) | |
| Davenport[a] et al. [3] | CT | 17,652 | All patients | 6.9<br>7.1 | | Single-center retrospective<br>Propensity score matching<br>Adjusted analysis in subgroups |
| | | 13,967 | CKD I + II | 5.4<br>5.5 | 1.00 (0.86–1.16 | |
| | | 2480 | CKD IIIa | 10.5<br>10.8 | 1.06 (0.82–1.38) | |
| | | 1089 | CKD IIIb | 16.7<br>14.2 | 1.40 (1.00–1.97) | |
| | | 116 | CKD IV–V | 36.4<br>19.4 | 2.96 (1.22–7.17)[‡] | |
| Ehrmann[a] et al. [6] | ICU | 292 | All patients (CKD 7%) | 5.5<br>5.5 | 1.57 (0.69–3.53) | Single-center retrospective<br>Propensity score matching |
| McDonald[a] et al. [7] | CKD + CT | 2440 | CKD III | 10<br>15 | 0.65 (0.41–0.89) | Single-center retrospective<br>Propensity score matched |
| | | | CKD IV–V | 21<br>20 | 1.14 (0.78–1.50) | |
| Hemmett et al. [8] | CT | 370 | | 10.7<br>9.1 | Adjusted *p* 0.11 | Multicenter retrospective<br>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<br>14 | 1.00 (0.79–1.26) | Single-center retrospective<br>Propensity score matched |
| | | 570 | eGFR ≤ 45 | 29<br>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<br>Propensity score matching<br>(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<br>Adjusted for Mehran score |
| | + Contrast | 94 | | 12.8 | | |
| | − Contrast | 105 | | 17.1 | | |

**Table 1 continued**

| | Setting | Sample size | Baseline kidney function | AKI<br>+ contrast (%)<br>− contrast (%) | OR (adjusted[b]) | Comments |
|---|---|---|---|---|---|---|
| Caspi[a] et al. [12] | STEMI | 1862 | | | 0.77 (0.56–1.06) | Single-center retrospective<br>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<br>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.

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**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.

Received: 13 September 2017 Accepted: 16 October 2017
Published online: 14 December 2017

**References**

1. James MT, Samuel SM, Manning MA, Tonelli M, Ghali WA, Faris P, Knudtson ML, Pannu N, Hemmelgarn BR (2013) Contrast-induced acute kidney injury and risk of adverse clinical outcomes after coronary angiography: a systematic review and meta-analysis. Circ Cardiovasc Interv 6:37–43
2. McDonald JS, McDonald RJ, Comin J, Williamson EE, Katzberg RW, Murad MH, Kallmes DF (2013) Frequency of acute kidney injury following intravenous contrast medium administration: a systematic review and meta-analysis. Radiology 267:119–128
3. Davenport MS, Khalatbari S, Cohan RH, Dillman JR, Myles JD, Ellis JH (2013) Contrast material-induced nephrotoxicity and intravenous low-osmolality iodinated contrast material: risk stratification by using estimated glomerular filtration rate. Radiology 268:719–728
4. McDonald JS, McDonald RJ, Williamson EE, Kallmes DF, Kashani K (2017) Post-contrast acute kidney injury in intensive care unit patients: a propensity score-adjusted study. Intensive Care Med 43:774–784
5. McDonald RJ, McDonald JS, Bida JP, Carter RE, Fleming CJ, Misra S, Williamson EE, Kallmes DF (2013) Intravenous contrast material-induced nephropathy: causal or coincident phenomenon? Radiology 267:106–118
6. Ehrmann S, Badin J, Savath L, Pajot O, Garot D, Pham T, Capdevila X, Perrotin D, Lakhal K (2013) Acute kidney injury in the critically ill: is iodinated contrast medium really harmful? Crit Care Med 41:1017–1026
7. McDonald JS, McDonald RJ, Lieske JC, Carter RE, Katzberg RW, Williamson EE, Kallmes DF (2015) Risk of acute kidney injury, dialysis, and mortality in patients with chronic kidney disease after intravenous contrast material exposure. Mayo Clin Proc 90:1046–1053
8. Hemmett J, Er L, Chiu HH, Cheung C, Djurdjev O, Levin A (2015) Time to revisit the problem of CIN? The low incidence of acute kidney injury with and without contrast in hospitalized patients: an observational cohort study. Can J Kidney Health Dis 2:38
9. Ehrmann S, Quartin A, Hobbs BP, Robert-Edan V, Cely C, Bell C, Lyons G, Pham T, Schein R, Geng Y, Lakhal K, Ng CS (2017) Contrast-associated acute kidney injury in the critically ill: systematic review and Bayesian meta-analysis. Intensive Care Med 43:785–794
10. Hinson JS, Ehmann MR, Fine DM, Fishman EK, Toerper MF, Rothman RE, Klein EY (2017) Risk of acute kidney injury after intravenous contrast media administration. Ann Emerg Med 69:577–586
11. Petek BJ, Bravo PE, Kim F, de Boer IH, Kudenchuk PJ, Shuman WP, Gunn ML, Carlbom DJ, Gill EA, Maynard C, Branch KR (2016) Incidence and risk factors for postcontrast acute kidney injury in survivors of sudden cardiac arrest. Ann Emerg Med 67:469–476
12. Caspi O, Habib M, Cohen Y, Kerner A, Roguin A, Abergel E, Boulos M, Kapeliovich MR, Beyar R, Nikolsky E, Aronson D (2017) Acute kidney injury after primary angioplasty: is contrast-induced nephropathy the culprit? J Am Heart Assoc 6:e005715
13. Wilhelm-Leen E, Montez-Rath ME, Chertow G (2017) Estimating the risk of radiocontrast-associated nephropathy. J Am Soc Nephrol 28:653–659
14. Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, Mintz GS, Lansky AJ, Moses JW, Stone GW, Leon MB, Dangas G (2004) A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. J Am Coll Cardiol 44:1393–1399
15. Sendeski MM (2011) Pathophysiology of renal tissue damage by iodinated contrast media. Clin Exp Pharmacol Physiol 38:292–299
16. Heyman SN, Brezis M, Reubinoff CA, Greenfeld Z, Lechene C, Epstein FH, Rosen S (1988) Acute renal failure with selective medullary injury in the rat. J Clin Invest 82:401–412
17. Zhao Y, Tao Z, Xu Z, Tao Z, Chen B, Wang L, Li C, Chen L, Jia Q, Jia E, Zhu T, Yang Z (2011) Toxic effects of a high dose of non-ionic iodinated contrast media on renal glomerular and aortic endothelial cells in aged rats in vivo. Toxicol Lett 202:253–260

18. Toso A, Leoncini M, Maioli M, Tropeano F, Di Vincenzo E, Villani S, Bellandi F (2014) Relationship between inflammation and benefits of early high-dose rosuvastatin on contrast-induced nephropathy in patients with acute coronary syndrome: the pathophysiological link in the PRATO-ACS study (Protective Effect of Rosuvastatin and Antiplatelet Therapy on Contrast-Induced Nephropathy and Myocardial Damage in Patients With Acute Coronary Syndrome Undergoing Coronary Intervention). JACC Cardiovasc Interv 7:1421–1429

19. Gocze I, Jauch D, Gotz M, Kennedy P, Jung B, Zeman F, Gnewuch C, Graf BM, Gnann W, Banas B, Bein T, Schlitt HJ, Bergler T (2017) Biomarker-guided intervention to prevent acute kidney injury after major surgery: the prospective randomized BigpAK study. Ann Surg. https://doi.org/10.1097/SLA.0000000000002485