Volume-Independent Renal Injury: Why Contrast-Induced Nephropathy Can Occur Even at Ultra-Low Contrast Doses

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Dear Editor,

I reviewed with great interest the article titled "Impact of Contrast Volume Used After Percutaneous Coronary Procedures in Patients at Risk for Contrast-Induced Nephropathy," authored by Freitas et al.[1] This post-hoc subgroup analysis, designed to assess contrast-induced nephropathy (CIN) risk management, provides clinically valuable data on the interaction between contrast type and volume, particularly in high-risk patient populations (n=2,268).[1]

CIN is one of the complications that we, as invasive cardiologists, anticipate and always keep in mind before starting a case. In fact, this feeling is greater than the expectation of technical complications that may occur during the procedure. Another point is that in some patients, even when a significant amount of contrast is used, there is no change in kidney values. Most cardiologists have experienced this situation. At this point, factors such as diabetes, advanced age, and existing kidney disease can cause the outcome to change even at low volumes by "modulating individual risk."[2]

Dividing the groups into 150 ml actually brings certain problems and a solution with it. First of all, the distribution of participants in the groups is quite different. Considering that the number of participants is also high, even the slightest difference can be expected to be significant. However, the interesting point is that, due to the negative outcome of the study, the difference in participants between groups suppresses this situation. Therefore, I believe that a lower volume cutoff should be applied for grouping, both to balance the ratio of participants between groups and to reduce the tendency for type 2 error.

Keywords

Contrast Media; Kidney Diseases; Percutaneous Coronary Intervention; Acute Kidney Injury

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In coronary procedures, it is quite difficult to estimate exactly how much contrast agent is actually used in real life. This is because a considerable amount of radiopaque agent is expelled within the injection line, within the catheter, within the indeflator, and during line flushing. Assuming that all of this does not enter the patient's body, the amount of contrast agent actively used is less. This volume can range from approximately 25-50 ml, and may be even higher in complex procedures and bypass patients. In this article, the average contrast volume for Group I is stated as 75.3 ± 28.0 mL. For Group II, it is 188.6 ± 46.9 mL. It can be said that at least 20-25 mL of these figures does not actually enter the patient's vascular bed but is only used for the system to function. Considering these lost volumes for both groups, we can assume that nearly three times as much effective contrast is used in Group 2.

The development of CIN with high contrast use is already known. The authors noted in the limitations that the number of patients using high contrast was relatively small. However, comparing groups with low volumes (<200-300 cc) is important for clinical practice. This is because statistical power was maintained despite all the constraints and analyses. Although the classic risk factors and their levels of effect for CIN development are well defined, it is known that CIN can develop even at very low volumes. The kidneys are vulnerable to high-volume contrast.[3] However, it highlights an important point in the results of this study. Despite a contrast difference of nearly threefold and despite the use of low-osmolar contrast, the absence of a significant difference between the two groups suggests that if a patient is going to develop CIN, he will; the importance of volume and media osmolarity is negligible. At this point, it can be considered that other players in the pathophysiology of CIN may be secretly more effective. It explains that the pathophysiology of CIN is not solely volume-dependent, and that processes such as renal medullary ischemia and tubular toxicity can be triggered even at very low doses in high-risk patients.[4] The 14.8% incidence of CIN observed in the low-volume group (Group I) supports the theory of volume-independent renal injury in high-risk patients reported in the literature.[4,5] If CIN develops in patients even at low volumes, it will be essential to take protective measures for every patient without question. For this reason, I believe it is time to set aside the importance of contrast type and volume for CIN development.

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References

1. Freitas RAP, Tanajura LFL, Sousa AGMR, Feres F, Costa JR. Impact of Contrast Volume Used after Percutaneous Coronary Procedures in Patients at Risk for Contrast-Induced Nephropathy. Arq Bras Cardiol. 2025;122(12):e20250270. doi: 10.36660/abc.20250270.
2. Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, et al. A Simple Risk Score for Prediction of Contrast-Induced Nephropathy after Percutaneous Coronary Intervention: Development and Initial Validation. J Am Coll Cardiol. 2004;44(7):1393-9. doi: 10.1016/j.jacc.2004.06.068.

3. Rear R, Bell RM, Hausenloy DJ. Contrast-Induced Nephropathy Following Angiography and Cardiac Interventions. Heart. 2016;102(8):638-48. doi: 10.1136/heartjnl-2014-306962.

4. Seeliger E, Sendeski M, Rihal CS, Persson PB. Contrast-Induced Kidney Injury: Mechanisms, Risk Factors, and Prevention. Eur Heart J. 2012;33(16):2007-15. doi: 10.1093/eurheartj/ehr494.

5. Mehran R, Dangas GD, Weisbord SD. Contrast-Associated Acute Kidney Injury. N Engl J Med. 2019;380(22):2146-55. doi: 10.1056/NEJMra1805256.

Reply

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Thank you sincerely for your interest in our article and for your careful and thoughtful reading of the manuscript. Letters like yours enrich the scientific debate and help us refine the interpretation of the data, especially on a topic as relevant and still controversial as contrast-induced nephropathy (CIN).

I fully agree with your observation that CIN remains a constant concern among cardiologists. It is a well-known fact that, in high-risk patients (diabetes, advanced age, pre-existing kidney disease), the threshold for developing kidney damage can be considerably lower, and individual factors strongly modulate the risk, as you rightly pointed out when citing individual risk modulation.

In the general population, the incidence of CIN is less than 2%.[1] In a study published in 2020, which evaluated 82,683 patients undergoing percutaneous coronary intervention, the observed incidence was 5.73%, a value similar to that reported by the NCDR CathPCI Registry, published in 2018.[2] It should be noted, however, that in patients classified as high-risk for developing this complication, rates can exceed 30%, depending on the number of risk factors present individually.[1,3,4]

The IDPC study was a randomized, single-center clinical trial that compared low-osmolarity (ioxaglate) and iso-osmolarity (iodixanol) iodinated contrast agents in the prevention of contrast-induced nephropathy (CIN) in high-risk patients undergoing diagnostic and/or therapeutic percutaneous coronary procedures. 2,268 patients with at least one high-risk factor (age >70 years, diabetes, non-dialysis chronic kidney disease, heart failure, cardiogenic shock, or acute coronary syndrome) were included. The primary outcome was the occurrence of CIN, defined as a relative increase >25% and/or absolute increase >0.5 mg/dL in creatinine between the 2nd and 5th day after contrast exposure. The overall incidence of CIN was 15%, with no significant difference between iso-osmolar (15.2%) and low-osmolarity (15.1%; P>0.99) contrast agents, including in subgroup analyses. There was also no difference in the need for dialysis within 30 days or mortality. It was concluded that, in high-risk patients, the occurrence of CIN was similar regardless of the type of contrast agent used.[5]

In our institution, as routine practice, diagnostic tests and coronary procedures have always been performed with the smallest possible amount of contrast. The average contrast used in the IDPC study was 89.5 mL.[5] For the analysis of the groups, logistic regression was applied to evaluate the occurrence of outcomes and their relationship with renal function. From the statistical analysis, it was identified that the cutoff point of 150 mL of contrast proved to be the most appropriate for this evaluation.

We know that adopting a cutoff point lower than 150 mL for group stratification resulted in unbalanced groups in size, but it is worth remembering that the populations are very similar in their characteristics. In fact, in post-hoc analyses like ours, the balance between groups is not always ideal, and a lower cutoff (for example, closer to 100–120 mL, or adjusted for body weight/creatinine) could provide greater granularity and perhaps greater statistical power to detect subtle differences in very low volumes. This is an inherent limitation of the design, and its criticism is pertinent; it reinforces the need for prospective studies with more refined pre-defined stratifications.

Regarding the issue of the effective volume of contrast that reaches the patient, your observation is extremely valid and is frequently underestimated in the literature. The 20–50 mL (or more in complex procedures) that remain in the injection line, catheter, do not actually contribute to systemic exposure. This point strengthens the discussion about the difficulty of estimating the real volume in clinical practice and reinforces the importance of techniques for minimizing wasted contrast (automated injection systems, low-volume catheters, etc.).

In the invasive cardiology service at IDPC, the routine in the hemodynamics room includes aspirating the residual contrast present in the catheter and injection line at the end of the procedure, returning it to the original vial, and subsequently accounting for the total volume administered at the end of the examination.

The most intriguing finding of our work[6] — and what motivated the title of your letter — was precisely the absence of a significant difference in the incidence of CIN between the groups, despite the substantial difference in volume and the use of low-osmolality contrast in both. The incidence of ~14.8% in the low-volume group is, in fact, important and aligns with reports in the literature of kidney injury in very high-risk patients, even with very low volumes (<50–100 mL). This supports the notion that, in certain patient profiles, CIN may have a significant volume-independent (or slightly volume-dependent) component, mediated by mechanisms

such as severe bone marrow ischemia, direct tubular toxicity in already vulnerable nephrons, endothelial dysfunction, oxidative stress, and inflammation — processes that can be initiated by minimal doses in predisposed individuals.[7]

However, it is important not to overgeneralize this conclusion. The literature still demonstrates a clear dose-response relationship in most scenarios[8,9]: volumes >100–140 mL (or >3–4 mL/kg or V/CrCl >3.7) consistently increase risk in multivariate analyses, especially in mixed populations. What your comment highlights—and rightly so—is that, at the extreme high risk, volume ceases to be the primary modulator, and other factors (hypoperfusion, anemia, peri-procedural hypotension, atherosclerotic microembolization, among others) may dominate the pathophysiology. In this subgroup, CIN may be more "contrast-associated" than strictly "contrast-induced," and protective measures (adequate hydration, withdrawal of nephrotoxic agents, use of high-intensity statins, rigorous minimization of contrast) should be universally applied, regardless of the planned volume.

In summary, this discussion brings a profound and necessary reflection on the topic, considering a comprehensive view of the role of contrast medium choice, individual vulnerability, and non-volumetric mechanisms. I agree that it is time to rethink preventive strategies as universal and not just volume-dependent.

Thank you again for your valuable contribution to the discussion.

References

1. Aspelin P, Aubry P, Fransson SG, Strasser R, Willenbrock R, Berg KJ, et al. Nephrotoxic Effects in High-Risk Patients Undergoing Angiography. N Engl J Med. 2003;348(6):491-9. doi: 10.1056/NEJMoa021833.
2. Amin AP, McNeely C, Spertus JA, Bach RG, Frogge N, Lindner S, et al. Incremental Cost of Acute Kidney Injury after Percutaneous Coronary Intervention in the United States. Am J Cardiol. 2020;125(1):29-33. doi: 10.1016/j.amjcard.2019.09.042.
3. Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, et al. A Simple Risk Score for Prediction of Contrast-İnduced Nephropathy after Percutaneous Coronary İntervention: Development and İnitial Validation. J Am Coll Cardiol. 2004;44(7):1393-9. doi: 10.1016/j.jacc.2004.06.068.
4. Budano C, Levis M, D'Amico M, Usmiani T, Fava A, Sbarra P, et al. Impact of Contrast-Induced Acute Kidney Injury Definition on Clinical Outcomes. Am Heart J. 2011;161(5):963-71. doi: 10.1016/j.ahj.2011.02.004.
5. Freitas RAP, Tanajura LF, Mehran R, Chamié D, Chaves A, Centemero M, et al. Ioxaglate versus IoDixanol for the Prevention of Contrast-Induced Nephropathy: The IDPC Trial. J Invasive Cardiol. 2023;35(6):E281-90. doi: 10.25270/jic/21.00249.
6. Freitas RAP, Tanajura LFL, Sousa AGMR, Feres F, Costa JR. Impact of Contrast Volume Used after Percutaneous Coronary Procedures in Patients at Risk for Contrast-Induced Nephropathy. Arq Bras Cardiol. 2025;122(12):e20250270. doi: 10.36660/abc.20250270.
7. Mehran R, Dangas GD, Weisbord SD. Contrast-Associated Acute Kidney Injury. N Engl J Med. 2019;380(22):2146-55. doi: 10.1056/NEJMra1805256.
8. Nie Z, Liu Y, Wang C, Sun G, Chen G, Lu Z. Safe Limits of Contrast Media for Contrast-Induced Nephropathy: A Multicenter Prospective Cohort Study. Front Med. 2021;8:701062. doi: 10.3389/fmed.2021.701062.
9. Liu Y, Chen SQ, Duan CY, Tan N, Chen JY, Zhou YL, et al. Contrast Volume-to-Creatinine Clearance Ratio Predicts the Risk of Contrast-Induced Nephropathy after Percutaneous Coronary Intervention in Patients with Reduced Ejection Fraction. Angiology. 2015;66(7):625-30. doi: 10.1177/0003319714548442.