Amino Acid Infusion for the Prevention of Acute Kidney Injury: Yet a Debatable Issue

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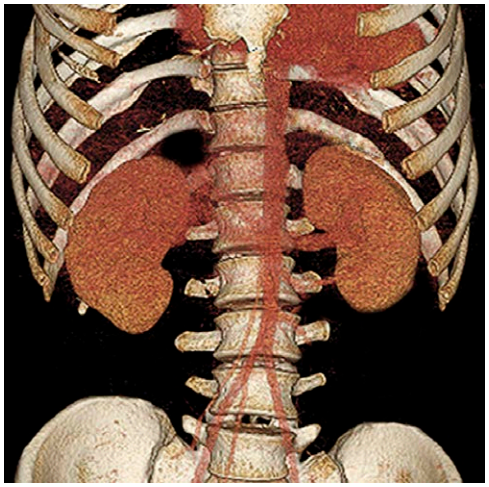
Acute kidney injury (AKI) is a common complication after cardiopulmonary bypass operations, occurring in 20 to 30% of patients, with up to 3% requiring dialysis.[1] Postoperative AKI increases morbidity and mortality, extends hospitalization course and expenses, and predicts the progression to chronic kidney disease (CKD).[1–3] Renal hypoperfusion and hypoxia with ischemia–reperfusion injury are believed to play a central role in the pathogenesis of AKI in these settings, along with additional renal insults, such as hemolysis, atheroemboli, inflammation, and the exposure to nephrotoxic medications.[1] Postoperative AKI in these settings is predictable, with most risk factors predisposing to renal hypoxia, including the hemodynamic status and respiratory function, diabetes, and preexisting CKD, as well as the duration of surgery and aortic cross-clamping.[1,4]



"Although robust evidence supports a renal functional advantage in patients given amino acid admixture after cardiac surgery, its impact on renal parenchymal oxygenation and integrity remains debated."

For years, studies of various interventions proposed to prevent or mitigate postcardiac surgery AKI have not been proven effective in clinical trials. The recently published Intravenous Amino Acid Therapy for Kidney Protection in Cardiac Surgery (PROTECTION) trial[5] has generated excitement among clinicians, because the trial found that patients who received perioperative continuous infusion of amino acid admixture had significantly lower incidence of in-hospital postoperative AKI (15%), as compared with patients who received perioperative placebo infusions (26.9%).[5] The PROTECTION trial enrolled 3,511 adult patients in an investigator-initiated, double-blind, multinational randomized clinical trial that was run by experienced researchers in accordance with a detailed preplanned study protocol. Enhanced renal blood flow and oxygen supply with the administration of amino acids formed the physiologic basis of this novel clinical intervention. A secondary analysis of the PROTECTION trial, reported in the current issue of Anesthesiology,[6] shows that patients undergoing cardiac surgery who received perioperative amino acid infusions *versus* placebo infusions experienced significantly decreased occurrence of postoperative AKI both in patients with preoperatively preserved kidney function (estimated glomerular filtration rate [eGFR] greater than 60 ml · min^{-1} · 1.73 m^{-2}) and in patients with reduced baseline eGFR (within the range of 30 to 59 ml · min^{-1} · 1.73 m^{-2}).

The findings of the PROTECTION trial are in line with those provided by a meta-analysis of 15 previously reported controlled studies, revealing AKI occurrence of 24.7 and 30.1% in patients given amino acid infusion and among control patients, respectively, with a significant risk reduction and a shorter hospitalization period.[7] Despite these encouraging results, supporting the perioperative administration of amino acids after cardiac surgery, a few questions and reservations outlined below deserve careful consideration.

Discrepancies between Declining GFR and the Extent of Renal Hypoxic Damage

As illustrated by animal studies and human autopsies, a poor correlation exists between the extent and distribution of tubular injury during AKI and its correlation with declining

Image: J. P. Rathmell.

This editorial accompanies the article on p. 818. This article has an audio podcast.

Accepted for publication February 19, 2025.

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 Anesthesiology 2025; 142:779–82. DOI: 10.1097/ALN.0000000000005432

<zdoi;10.1097/ALN.0000000000005432>

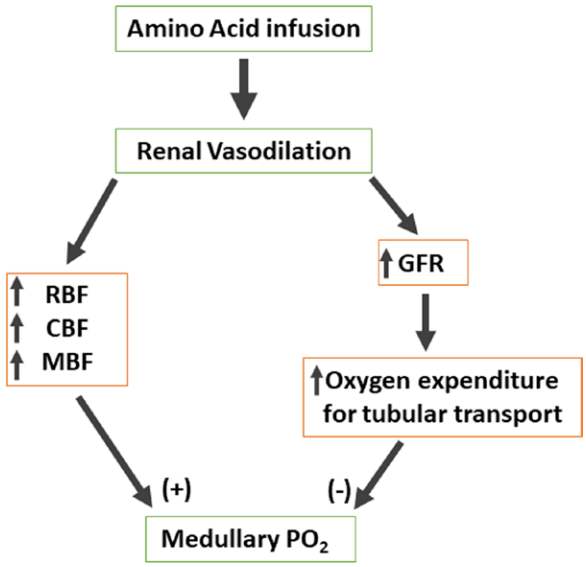

Fig. 1. Administration of amino acids admixture attenuates the risk of acute kidney injury after cardiac bypass surgery, as defined by reduction of estimated glomerular filtration rate (eGFR). This intervention causes afferent arteriolar vasodilation, enhancing renal blood flow (RBF) and GFR. However, these changes may endanger renal parenchymal integrity, because enhancing GFR with amino acid infusion intensifies medullary transport workload and may lead to hypoxic tubular injury. A dichotomy may exist between changes in glomerular hemodynamics and the extent of true injury, because possible tubular injury may be concealed by the recruitment of renal function reserve and the inactivation of a tubulo-glomerular feedback response to pending medullary hypoxic damage. CBF, cortical blood flow; MBF, medullary blood flow.

GFR.[8,9] To a large extent, this reflects the activation of a tubulo-glomerular feedback response to evolving distal tubular injury, with afferent arteriolar vasoconstriction and diminished GFR. The physiologic logic in this response is that diminished GFR reduces solute delivery to the distal nephron, with consequent reduction of hypoxic stress by the attenuation of regional oxygen consumption for tubular transport.

Does Improved GFR with Amino Acid Infusion Truly Reflect Renal Parenchymal Salvage?

A high-protein meal or infusion of amino acids leads to glomerular afferent arteriolar vasodilation, with enhanced renal blood flow. This acute physiologic response is mediated by nitric oxide and prostaglandins, with recruitment of renal functional reserve, manifested by increased GFR.[10] It has been proposed that improved renal blood flow with amino acid infusion could improve renal oxygen delivery to the kidney and thus reduce hypoxic renal injury (fig. 1). Furthermore, afferent arteriolar vasodilation caused by this procedure could also counteract the activation of a tubulo-glomerular feedback in response to evolving tubular injury after surgery, preventing afferent arteriolar vasoconstriction and reduced GFR. However, preservation of GFR after cardiac surgery with amino acids does not necessarily reflect renal parenchymal protection against hypoxic\ischemic damage but rather represents a nonspecific enhancement of GFR proportional to the degree of renal functional reserve. Furthermore, inactivation of the tubulo-glomerular feedback response may enhance solute delivery to the distal nephron and may intensify medullary hypoxia and hypoxic damage (fig. 1). The only way to unequivocally claim renal protection with amino acid infusion might likely be by the determination of biomarkers of kidney injury, an experimental tool that regretfully has not been adopted in the PROTECTION trial.[5]

Redaelli *et al.*[6] claim that improved eGFR with amino acid infusion in patients with CKD was comparable to that among patients without CKD, in favor of a true kidney parenchymal protection. This assumption is based on the anticipation that patients with CKD with reduced renal functional reserve will display a blunted glomerular hemodynamic response to amino acid infusion, but this statement does not address the impact of reversal of activated tubulo-glomerular feedback and is not clearly illustrated by comparing the increments in eGFR with amino acids in patients without and with CKD, stratified by their baseline CKD as defined in the study. Furthermore, patients with advanced CKD (eGFR less than 30 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$), essentially lacking renal functional reserve, were not included in the PROTECTION trial. Last, representation of daily changes in eGFR extend only throughout the 72 h of amino acid infusion (fig. 2 in Redaelli's report[6]), possibly missing a later decline in GFR in amino acid-treated patients at the conclusion of this treatment. Therefore, regretfully, it is currently impossible to unequivocally state that the administration of amino acids preserves renal parenchymal integrity, without the determination of biomarkers of tubular injury.

A Plausible Risky Impact of Amino Acid Infusion on Renal Oxygen Expenditure

As stated in the previous section, the assumption that enhanced renal blood flow with amino acid infusion will improve renal oxygenation does not consider the impact of amino acid infusion on oxygen consumption for renal tubular transport activity (fig. 1). Boosting GFR with amino acid infusion enhances solute delivery for reabsorbtion along the nephron. This might be particularly important in the physiologically hypoxic outer medulla, characterized by a limited blood supply through vasa recta, barely sufficient for regional oxygen requirement for tubular transport.[11] Indeed, measures that increase renal and medullary blood flow, such as the infusion of dopamine do not improve medullary oxygenation, likely as regional tubular transport load increases in parallel.[12] This might explain the lack of renal salvage with dopamine and other agents so-far studied that kick up GFR in management of AKI. In this line of

logic, the renal medulla might be endangered by enhanced GFR and consequent augmented oxygen extraction, noted in humans given amino acids at the conclusion of cardiac surgery (fig. 1).[13]

With that in mind, data regarding direct measurements of renal oxygenation during amino acid infusion are sparse and contradicting. The infusion of glycine was found to intensify the physiologic outer medullary hypoxia, reaching average Po_2 levels as low as 13 mmHg in anesthetized rats, despite increased renal blood flow.[14] This conceivably explains a marked intensification of renal parenchymal hypoxic injury with glycine infusion, noted in anesthetized rats undergoing renal ischemia and reperfusion or subjected to a model of radiocontrast nephropathy with outer medullary hypoxic injury.[14] By contrast, amino acid admixture given to awake instrumented sheep resulted in improved cortical and medullary oxygenation, along with enhanced regional microcirculation, despite a rise in GFR, sodium reabsorption and oxygen utilization.[15] The diverse outcomes in these two animal models regarding renal parenchymal oxygenation might be explained by various factors, including the type of given amino acid (glycine alone *vs.* amino acid admixture) different species used, the impact of anesthesia, or the degree of reversal of efferent arteriolar vasoconstriction with amino acids (attenuating the rise in GFR and improving downstream microcirculation), that might be related to different levels of activation of the renin-angiotensin axis.[10]

The impact of amino acid infusion on oxygen consumption for tubular transport and on medullary oxygenation might be especially important in patients with advanced CKD (eGFR less than 30 ml · min^{-1} · 1.73 m^{-2}), not included in the PROTECTION trial. This population is particularly prone to AKI in general and specifically to hypoxic AKI, as shown in patients with radiocontrast-associated AKI.[16]

Thus, at present, with no data regarding renal parenchymal integrity, such as the assessment of biomarkers of tubular cell injury, the ability of amino acid infusion to improve medullary oxygenation and to attenuate tubular hypoxic/ischemic injury after cardiac surgery remains speculative, especially in high-risk patients with compromised medullary oxygenation.

Plausible Declining Impact of Amino Acid Infusion in Advanced CKD

It is anticipated that the effect of amino acid infusion on renal microcirculation and oxygen delivery on the one hand and on oxygen consumption for tubular transport on the other hand will diminish as baseline GFR and renal functional reserve declines. The data now provided by Redaelli *et al.*,[6] although showing prevention of AKI, do not fully address this issue, because the increments in eGFR noted with amino acid infusion are not subdivided according to the baseline eGFR groups and compared with patients with preserved kidney function and with CKD patients with eGFR less than 30 ml · min^{-1} · 1.73 m^{-2}. If indeed GFR increments are comparable in these subgroups, one may look for an additional plausible extrinsic renal functional protective effect, such as a better cardiac performance, related to improved myocardial oxidative metabolism and hastened myocardial recovery postischemia.[17]

A Plausible Impact of Other Confounders

Patients included in the PROTECTION project were likely subjected to additional interventions and drugs that substantially affect renal medullary oxygenation and parenchymal integrity, including pressors and loop diuretics. Particularly furosemide has a profound impact on medullary oxygenation, blocking sodium uptake and oxygen consumption in medullary thick ascending limbs, with a dramatic increase in medullary oxygenation, despite reduction in regional blood flow.[18] Accordingly, furosemide substantially attenuated outer medullary tubular injury in hypoxic AKI model in rats,[19] and if given to patients in the PROTECTION trial, it could avert a potential decline in medullary oxygenation and medullary hypoxic injury caused by amino acid–related GFR enhancement. With that in mind, combined amino acid infusion and furosemide seems a logic combination for the preservation of renal function and morphology after cardiac surgery, but that, of course, currently remains speculative.

Conclusions

In sum, although robust evidence supports a renal functional advantage in patients given amino acid admixture after cardiac surgery, its impact on renal parenchymal oxygenation and integrity remains debated. The somewhat smaller incidence in the need for renal replacement therapy in the amino acid group is reassuring. However, because this intervention is potentially harmful, with the development of medullary hypoxic tubular damage that might be concealed by improved renal hemodynamics, independent of tissue injury, further studies are clearly required for safety issues, conceivably with the use of urine and plasma biomarkers of AKI, especially in patients with more advanced CKD. We believe that smaller cohorts of patients are needed for such safety studies, looking at AKI biomarkers, before fully adopting the novel intervention of perioperative amino acid infusion in patients with eGFRs greater than 30 ml · min^{-1} · 1.73 m^{-2}. These studies might be complemented by monitoring patients' urine oxygenation, which apparently can be used as a practical surrogate for measures determining renal medullary oxygenation.[20] Excluding the potential risk of enhancing medullary hypoxia and damage with perioperative amino acid infusion with such rather small studies will allow exploring this intervention in patients with eGFR less than 30 ml · min^{-1} · 1.73 m^{-2} as well.

Research Support

Support was provided solely from institutional and/or departmental sources.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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References

1. Cheruku SR, Raphael J, Neyra JA, Fox AA: Acute kidney injury after cardiac surgery: Prediction, prevention, and management. Anesthesiology 2023; 139:880–98
2. Rydén L, Sartipy U, Evans M, Holzmann MJ: Acute kidney injury after coronary artery bypass grafting and long-term risk of end-stage renal disease. Circulation 2014; 130:2005–11
3. Li Z, Fan G, Zheng X, et al.: Risk factors and clinical significance of acute kidney injury after on-pump or off-pump coronary artery bypass grafting: A propensity score-matched study. Interact Cardiovasc Thorac Surg 2019; 28:893–9
4. Jucá FG, Freitas FL, Goncharov M, et al.: Difference between cardiopulmonary bypass time and aortic cross-clamping time as a predictor of complications after coronary artery bypass grafting. Braz J Cardiovasc Surg 2024; 39:e20230104
5. Landoni G, Monaco F, Ti LK, et al.; PROTECTION Study Group: A randomized trial of intravenous amino acids for kidney protection. N Engl J Med 2024; 391:687–98
6. Baiardo Redaelli M, Monaco F, Bradic N, et al.; for the PROTECTION Study Group Collaborators: Amino acid infusion for kidney protection in cardiac surgery patients with chronic kidney disease: A secondary analysis of the PROTECTION trial. Anesthesiology 2025; 142:818–28
7. Pruna A, Losiggio R, Landoni G, et al.; for the Protection Study Group: Amino acid infusion for perioperative functional renal protection: A meta-analysis. J Cardiothorac Vasc Anesth 2024; 38:3076–85
8. Goldfarb M, Rosenberger C, Abassi Z, et al.: Acute-on-chronic renal failure in the rat: Functional compensation and hypoxia tolerance. Am J Nephrol 2006; 26:22–33
9. Heyman SN, Rosenberger C, Rosen S: Experimental ischemia–reperfusion—Biases and myths: The proximal vs. distal hypoxic tubular injury debate revisited. Kidney Int 2010; 77:9–16
10. Jufar AH, Lankadeva YR, May CN, Cochrane AD, Bellomo R, Evans RG: Renal functional reserve: From physiological phenomenon to clinical biomarker and beyond. Am J Physiol Regul Integr Comp Physiol 2020; 319:R690–702
11. Brezis M, Rosen S: Hypoxia of the renal medulla—Its implications for disease. N Engl J Med 1995; 332:647–55
12. Heyman SN, Kaminski N, Brezis M: Dopamine increases medullary blood flow without improving regional hypoxia. Exp Nephrol 1995; 3:331–7
13. Jeppsson A, Ekroth R, Friberg P, et al.: Renal effects of amino acid infusion in cardiac surgery. J Cardiothorac Vasc Anesth 2000; 14:51–5
14. Heyman SN, Brezis M, Epstein FH, Spokes K, Rosen S: Effect of glycine and hypertrophy on renal outer medullary hypoxic injury in ischemia reflow and contrast nephropathy. Am J Kidney Dis 1992; 19:578–86
15. Jufar AH, Evans RG, May CN, et al.: The effects of recruitment of renal functional reserve on renal cortical and medullary oxygenation in non-anesthetized sheep. Acta Physiol (Oxf) 2023; 237:e13919
16. Gorelik Y, Bloch-Eisenberg N, Heyman SN, Khamaisi M: AKI following radiocontrast-enhanced computerized tomography in hospitalized patients with advanced renal failure: A propensity score matching analysis. Invest Radiol 2020; 55:677–87
17. Engelman RM, Rousou JA, Flack JE III, Iyengar J, Kimura Y, Das DK: Reduction of infarct size by systemic amino acid supplementation during reperfusion. Thorac Cardiovasc Surg 1991; 101:855–9.
18. Brezis M, Agmon Y, Epstein FH: Determinants of intrarenal oxygenation. I. Effects of diuretics. Am J Physiol 1994; 267:F1059–62
19. Heyman SN, Brezis M, Greenfeld Z, Rosen S: Protective role of furosemide and saline in radiocontrast-induced acute renal failure in the rat. Am J Kidney Dis 1989; 14:377–85
20. Sgouralis I, Kett MM, Ow CPC, et al.: Bladder urine oxygen tension for assessing renal medullary oxygenation in rabbits: Experimental and modeling studies. Am J Physiol Regul Integr Comp Physiol 2016; 311:R532–44