In conclusion, Kamenshchikov and colleagues are to be congratulated for highlighting the promise of nitric oxide for renal protection in adult cardiac surgery. They have identified this versatile agent as a possible magic bullet for renal rescue as we continue our voyage to piece together the complex puzzle of AKI associated with cardiac surgery.

References

- Engelman DT, Schwann TA. Commentary: a little is way too much: what we have learned about perioperative acute kidney injury. *J Thorac Cardiovasc Surg*. January 21, 2020 [Epub ahead of print].
- Cho JS, Shim J, Lee S, Song JW, Choi N, Lee S, et al. Chronic progression of cardiac surgery associated acute kidney injury: intermediary role of acute kidney disease. *J Thorac Cardiovasc Surg*. November 6, 2019 [Epub ahead of print].
- Kramer RS. Commentary: Is acute kidney injury after cardiac surgery the canary in the mineshaft? *J Thorac Cardiovasc Surg*. December 12, 2019 [Epub ahead of print].
- Di Bacco L, Montisci A, Miceli A. Commentary: acute kidney injury: the one-million pieces puzzle. *J Thorac Cardiovasc Surg*. 2019;157:2367-8.
- Montisci A, Travaglini S, Miceli A. Commentary: the lack of a magic bullet. *J Thorac Cardiovasc Surg*. 2019;157:2352-3.
- Augoustides JG. Serum creatinine as a perioperative biomarker: a challenge for perioperative management and an opportunity for the Cardiothoracic Surgery Trials Network. *J Thorac Cardiovasc Surg*. 2012;143:523-4.
- Chuey STH, Hwang NC. Acute kidney injury after cardiac surgery: a narrative review of the literature. *J Cardiothorac Vasc Anesth*. 2019;33:1122-38.
- Kamenshchikov NO, Podoksenov YK, Anfinogenova YJ, Kozlov BN, Svirko YS, Pekarskiy SE, et al. Nitric oxide delivery during cardiopulmonary bypass reduces acute kidney injury: randomized trial. *J Thorac Cardiovasc Surg*. 2022;163:1393-403.e9.
- Hessel EA. What's new in cardiopulmonary bypass? *J Cardiothorac Vasc Anesth*. 2019;33:2296-326.
- Lama TT, Berra L, Zapol WM. The role of nitric oxide in preventing cardiopulmonary bypass-associated acute kidney injury. *J Cardiothorac Vasc Anesth*. 2020;34:850-1.
- Lei C, Berra L, Rezoagli E, Yu B, Dong H, Yu S, et al. Nitric oxide decreases acute kidney injury and stage 3 chronic kidney disease after cardiac surgery. *Am J Respir Care Crit Care Med*. 2018;198:1279-87.
- Marrazzo F, Spina S, Zadek F, Lama T, Xu C, Larson G, et al. Protocol of a randomized controlled trial in cardiac surgical patients with endothelial dysfunction aimed to prevent postoperative acute kidney injury by administering nitric oxide gas. *BMJ Open*. 2019;9:e026848.
- Hi J, Spina S, Zadek F, Kamenshchikov NO, Bittner EA, Pedemonte J, et al. Effect of nitric oxide on postoperative acute kidney in patients who underwent cardiopulmonary bypass: a systematic review and meta-analysis with trial sequential analysis. *Ann Intensive Care*. 2019;9:129.
- Crawford JH, Townsley MM. Steroids for adult and pediatric cardiac surgery: a clinical update. *J Cardiothorac Vasc Anesth*. 2019;33:2039-45.
- Augoustides JG. Beating the clostridium difficile infection—insights from the Cardiothoracic Surgery Trials Network. *J Thorac Cardiovasc Surg*. 2017;155:679-80.

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Commentary: Just say NO!

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One nitrogen atom covalently bonded to 1 oxygen atom is nitric oxide. Add 1 more nitrogen and you have laughing gas—a medically useful compound produced by humans in large amounts. Add an oxygen atom to nitric oxide and you have smog—another gas produced by humans in abundance, unfortunately. Well known for many years to industrial chemical engineers, nitric oxide's biologic function as an important

Capsules stuffed with arginine, ready to raise your nitric oxide level.

CENTRAL MESSAGE

Nitric oxide delivered through the oxygenator on CPB decreases AKI.

molecular signal in systems regulating vascular tone was elucidated in the 1980s, earning it *Science* magazine's "Molecule of the Year" award in 1992 and the 1998 Nobel Prize in Physiology or Medicine for 3 Americans: Furchott, Ignarro, and

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Murad. As a small, highly reactive free radical, nitric oxide—synthesized from arginine in vascular endothelium—passes freely through cell membranes to relax nearby smooth muscle cells before vanishing in a few seconds, making it perfect for moment-to-moment modulation of vascular tone. Nitric oxide became a drug in the 1990s with the realization that if inhaled in minute amounts (20–40 PPM), it will selectively dilate the pulmonary vascular bed and disappear before reaching the systemic vessels. Although only Food and Drug Administration-approved for persistent pulmonary hypertension in newborn infants, much, if not most, nitric oxide is used in adults to treat pulmonary hypertension and its adverse effects.

Kamenshchikov and colleagues¹ studied another, even more novel way to use nitric oxide therapeutically. They gave nitric oxide to adult cardiac surgery patients at moderate risk for acute kidney injury (AKI) by blending it with the fresh gas flowing into the oxygenator of the cardiopulmonary bypass (CPB) circuit. In their randomized trial, blinded except for the perfusionists, with 48 patients in each arm, the treatment group had half as much AKI postoperatively: 20.8% versus 41.6% ($P = .023$). The treatment group also made more urine on CPB and had significantly lower levels of urinary neutrophil gelatinase-associated lipocalin, a well-known marker for acute renal injury. They also measured toxic metabolites of nitric oxide, which, as one would expect, were higher in the treatment group during CPB, but which fell quickly back to baseline. This study is

important because AKI after cardiac surgery is common and, even when mild, associated with decreased long-term survival.² The renal protective effect of nitric oxide during cardiac surgery has been observed before,³ but this study not only confirms that the benefit is real, it describes a practical and elegant method to deliver nitric oxide to the kidneys exactly when it is needed: on CPB. Among the concerns of using nitric oxide is cost, especially in the United States. The technique described in this study provides a clear means to limit its use to a relatively short, well-defined duration: bypass time. The technique also is attractive because, by keeping the nitric oxide delivery system in the operating room, it avoids the complexities of transport and setting up in an intensive care unit. This study is an important step forward in the ongoing battle against perioperative AKI and will hopefully inspire larger trials aimed at investigating long-term outcomes and cost-effectiveness.

References

1. Kamenshchikov NO, Podoksenov YK, Anfinogenova YI, Kozlov BN, Svirko YS, Pekarskiy SE, et al. Nitric oxide delivery during cardiopulmonary bypass reduces 1 acute kidney injury: randomized trial. *J Thorac Cardiovasc Surg.* 2022;163:1393–403.e9.
2. Bouma HR, Mungroop HE, de Geus AF, Huisman DD, Nijsten MWN, Mariani MA, et al. Acute kidney injury classification underestimates long-term mortality after cardiac valve operations. *Ann Thorac Surg.* 2018;106:92–8.
3. Lei C, Berra L, Rezoagli E, Yu B, Dong H, Yu S, et al. Nitric oxide decreases acute kidney injury and stage 3 chronic kidney disease after cardiac surgery. *Am J Respir Crit Care Med.* 2018;198:1279–87.