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Commentary: Nitric oxide and acute kidney injury: Understanding the puzzle of renal rescue after cardiac surgery

John G. Augoustides, MD, FASE, FAHA

Acute kidney injury (AKI) is an independent predictor of significant morbidity and mortality after cardiac surgery.^{1,2} Consequently, renal rescue is a priority in perioperative management.³ Unfortunately, knowledge gaps in the pathogenesis of AKI have persisted, prompting calls for magic bullets to help us understand this complex puzzle.⁴⁻⁶ One of the pieces in this puzzle is renal ischemia from multiple mechanisms, including depletion of nitric oxide due to endothelial dysfunction and hemolysis.⁷⁻¹⁰

The timely trial by Kamenshchikov and colleagues⁸ in this issue of the *Journal* has evaluated nitric oxide for renal rescue in elective adult cardiac surgery with cardiopulmonary bypass. In this trial, patients at moderate risk for AKI were randomized to nitric oxide therapy at a dose of 40 parts per million during cardiopulmonary bypass.⁸ Exposure to nitric oxide significantly decreased AKI and release of the renal injury biomarker, neutrophil gelatinase-associated lipocalin.⁸

How might these intriguing findings inform our approach to AKI? In a recent randomized trial from China (N = 244), nitric oxide therapy during cardiopulmonary bypass and for the first 24 postoperative hours significantly reduced AKI throughout the first postoperative year.¹¹ These convincing results have prompted a trial in the United States to evaluate whether these nephroprotective effects of nitric oxide are also relevant in the West.¹² The data from Kamenshchikov

The puzzle of acute kidney injury after cardiac surgery.

CENTRAL MESSAGE

Acute kidney injury after cardiac surgery is important. Nitric oxide therapy has great promise for renal rescue, helping us piece together the complex puzzle of acute kidney injury in this setting.

and colleagues therefore strengthen the hypothesis that nitric oxide protects the kidney after cardiac surgery, suggesting that renal rescue with nitric oxide may well be a generalizable perioperative intervention for our patients.⁸⁻¹¹

What are our options in light of the literature? A recent meta-analysis (N = 579; 5 trials, including data from Kamenshchikov and colleagues) demonstrated that nitric oxide therapy significantly decreased the risk of AKI, especially when commenced early during cardiopulmonary bypass.¹³ Although the evidence to date is suggestive, further trials are required to clarify pharmacologic aspects of nitric oxide therapy for renal rescue such as dose, timing, and duration.⁷⁻¹³

So, where do we go from here? There is a critical mass of positive data to support an adequately powered multicenter trial to test the potential for renal rescue with nitric oxide in cardiac surgery with cardiopulmonary bypass akin to the escalation of clinical trials for the evaluation of steroids in adult cardiac surgery.¹⁴ Given the promise of the nitric oxide trials to date and the central importance of AKI, the priority for a high-quality, large randomized trial may be an opportunity for the Cardiothoracic Surgery Trials Network.¹⁵ Further trials could also address not only the optimal perioperative dosing strategy for nitric oxide but also its nephroprotective potential in pediatric cardiac surgery (eg, one neonatal trial already listed—full details available at www.clinicaltrials.gov with trial identifier NCT03946462, last accessed April 5, 2020).

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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.

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Commentary: Just say NO!

Jack S. Shanewise, MD, FASE

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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