Nitric Oxide and Kidney Injury after Cardiac Surgery: A Solution Looking for a Problem

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The diagnosis of acute kidney injury (AKI) is common after cardiac surgery, particularly in patients with preexisting chronic kidney disease.[1] The incidence of AKI in this population remains high, leading to increased morbidity, mortality, and healthcare costs.[2] Although the 2012 Kidney Disease Improving Global Outcomes guidelines for staging AKI within 7 days has been validated for medication interventions in cardiac surgery, serum creatinine kinetics alone modestly reflect renal tubular injury. While staging is important and the majority of patients with AKI stage 1 do not develop long-term adverse outcomes, biomarker analysis may be particularly valuable in clinical trials (especially positive trials) to help bridge the gap between clinical findings and mechanistic underpinnings.

"Exogenous administration of NO in cardiothoracic surgery has been controversial, mainly rooted around cost concerns, prolonged usage reducing endogenous NO generation, and availability of alternative pulmonary-selective agents with similar outcome profiles."

In this issue of Anesthesiology, Kamenshchikov *et al.*[3] report results from the DEFENDER (Perioperative Nitric oxiDE-conditioning, Produced by Plasma-chemical Synthesis Technology, For prevEnt Acute kidNey Injury During carDiac surgEry in Patients With chRonic Kidney Disease) trial, a single-center, randomized placebo-controlled trial of NO to reduce AKI in adult patients with chronic kidney disease undergoing elective cardiac surgery using cardiopulmonary bypass (CPB). Nitric oxide (80ppm) was delivered using a plasma chemical synthesis device currently available in Russia (Tianox device, Russian Federal Nuclear Center—All-Russian Research Institute of Experimental Physics, Russia). Either air mixture or 80 ppm NO delivery was initiated through the lungs after tracheal intubation, continued *via* oxygenator while on CPB, and delivered through endotracheal tube into the postoperative period for as long as 6 h, discontinuing delivery at extubation. The primary outcome was AKI development of any stage within 7 days after surgery. The study found that AKI development was significantly lower in the NO group (23.5%) compared to the control group (39.7%), with a relative risk of 0.59 (95% CI, 0.35 to 0.99). Additionally, 6 months after surgery, the estimated glomerular filtration rate was modestly higher in the NO group compared with placebo ($50\,\mathrm{ml} \cdot \mathrm{min}^{-1} \cdot 1.73\ \mathrm{m}^{-2}$ [45 to 54] *vs.* $45\,\mathrm{ml} \cdot \mathrm{min}^{-1} \cdot 1.73\ \mathrm{m}^{-2}$; $P = 0.038$). Importantly, the incidence of composite major adverse kidney events (including death, renal replacement therapy, and 25% decrease in estimated glomerular filtration rate) did not differ between groups. Serial stress biomarkers of AKI were also compared in 40 patients per group, and no differences were found in levels of urine neutrophil gelatinase–associated lipocalin, urinary kidney injury molecule-1, interleukin-18, serum cystatin C, and intestinal fatty acid–binding protein.[3]

There have been two other notable positive trials to date that endorse NO therapy during CPB and afterward for kidney protection. This includes a previous trial by Kamenshchikov *et al.*[4] that randomized 96 patients at moderate risk for AKI to NO at 40 ppm or placebo administered in similar fashion as the current study and showed reduced

Image: J. P. Rathmell.

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AKI development in the NO group (20.8%, N = 10 for the NO group *vs.* 41.6%, N = 20 for the placebo group; relative risk, 0.5; 95% CI, 0.26 to 0.95). Urine neutrophil gelatinase–associated lipocalin at 4 h after surgery was also lower in the NO group compared with placebo. In addition, Lei *et al.*[5] randomized 244 patients to 80 ppm NO or nitrogen gas during CPB and for 24 h after surgery to find reduced AKI in the NO group (50% *vs.* 64%; relative risk, 0.78; 95% CI, 0.62 to 0.97). Recognizing that nitric oxide has several potential clinical upsides, why is this agent not readily delivered in cardiac surgical practice across the world?

The late Dr. Warren Zapol provided an impactful first-hand account in the Journal on pioneering the delivery of exogenous NO in the newborn with persistent pulmonary hypertension.[6] He also highlighted how a highly purified, costly form of NO had been synthesized in recent years, using a chemical reaction between aqueous nitric acid and gaseous sulfur dioxide while requiring a complex, cylinder-based, delivery device (U.S. patent 5670127A). In the current study, the Tianox device synthesizes purified NO within a high-energy plasma environment that allows for nitrogen and oxygen in atmospheric air to readily react, also creating a highly purified, cost-effective form of NO for medical therapy.[3] These two approaches to NO synthesis were previously found to be similar in the ability to reduce pulmonary vascular resistance in six cardiac catheterization laboratory patients at a single center.[7] Mechanistically, NO vasodilates *via* activation of soluble guanylate cyclase in smooth muscle cells and is an avid scavenger of free hemoglobin to reduce tissue oxidative stress from hemolysis. Nitric oxide also binds with hemoglobin to enhance local vasodilation and regulate tissue oxygen delivery *via* *S*-nitrosohemoglobin, which can be measured in the blood and has been linked to renal injury after CPB.[8]

Exogenous administration of NO in cardiothoracic surgery has been controversial, mainly rooted around cost concerns,[9] prolonged usage reducing endogenous NO generation,[10] and availability of alternative pulmonary-selective agents with similar outcome profiles.[11] While the current trial was conducted in Russia, the North American market for commercial NO procurement is experiencing a watershed moment, realizing a gradual departure from pricing set by a single supplier that once dominated the market from lack of both competition and randomized trials.[12]

Regarding generalizability of DEFENDER results, there is often a knee-jerk reflex to repudiate single-center clinical trials. However, protocols are key to understanding the applicability of trial results for an after-market medication in complex patient populations that may be challenging to accomplish a multicenter investigation. For this reason, other centers are encouraged to take under advisement when considering implementation the NO delivery device, NO dosage, CPB plus invasive airway delivery, delivery duration, patient population, and cardiac surgery subtype.

There is a need to better standardize NO delivery by dosing, treatment duration, and weaning parameters once treatment is no longer necessary. In a recent systematic review of 27 clinical trials of NO in cardiac surgery, Yan *et al.*[13] found that maximum dosing generally included 20 and 40 ppm, and NO was commonly initiated after CPB separation *via* mechanical ventilation. This review included a recent, large randomized double-blind trial of NO *versus* aerosolized epoprostenol in major cardiac surgery, in which NO was initiated at a maximum dose of 20 ppm after CPB separation, continuously administered for almost 4 days and then weaned off once prespecified criteria were met using a common approach (hourly decrease in NO in ppm: 20 → 10 → 5 → 1 → 0).[11] In acute respiratory distress syndrome, continuous administration of NO 10 ppm by inhalation led to sensitization by day 4, with 1 ppm achieving better oxygenation than leaving patients on 10 ppm.[14] Therefore, it is reasonable to consider lower NO dosing for oxygenation and pulmonary arterial pressure modulation since NO treatment duration may be prolonged. Additionally, dose responsiveness to NO for indications of oxygenation or pulmonary vasodilation can be readily measured by available clinical monitoring. While the authors have demonstrated that higher NO dosing for short durations can be safely administrated, dose-response studies during prolonged use are needed in adult cardiac surgery to evaluate optimal NO dosing and duration for the AKI indication, especially as more novel biomarkers of renal function emerge that can directly measure changes in tissue oxygenation before, during, and after therapeutic interventions.

Does the biomarker analysis from DEFENDER suggest that NO therapy offers mechanistic advantages that explain the difference in the primary outcome? Do we need better endpoints for determining tubular injury and defining (subclinical) AKI development in moderate risk cardiac surgical patients? A lofty goal would be to leverage willing and existing multicenter trial networks to determine the impact of NO on a composite kidney injury definition that includes patient-centered outcomes, clinical endpoints, and more novel renal biomarkers that may directly signal tubular injury. In parallel, economic concerns about the high costs of NO therapy pressurize this topic, and if higher NO dosing for AKI mitigation is needed, how can we create the necessary conditions to generate better price points for NO procurement? Until that time, Kamenshchikov *et al.*[3] provide more compelling evidence that perioperative NO therapy could potentially DEFEND against kidney injury associated with adult cardiac surgery.

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Competing Interests

Dr. Fielding-Singh reports research funding paid to his institution unrelated to the current work from SeaStar Medical, Calcimedica, Octapharma, and the National Institute on Aging (Bethesda, Maryland). Dr. Ghadimi reports a patent pending relevant to current work: U.S. patent 2024/0066250 A1.

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