Commentary: Encouraging findings for the renal-protective effect of nitric oxide administration during cardiopulmonary bypass

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Acute kidney injury (AKI) remains a persistent source of morbidity and mortality following cardiac surgery with cardiopulmonary bypass (CPB). Although the pathophysiology of AKI is multifactorial, hemolysis during CPB represents 1 important mechanism because it leads to depletion of vascular nitric oxide, a potent vasodilator responsible for modulating organ perfusion and vascular homeostasis. Decreased nitric oxide in the bloodstream can lead to organ malperfusion, inflammation, oxidative stress, and direct tubular injury, all of which can contribute to AKI after cardiac surgery. Provision of supplemental exogenous nitric oxide via the CPB oxygenator is one promising new therapy to potentially mitigate CPB-associated AKI.

Greenberg and colleagues present an animal study that evaluated the renal-protective effect of nitric oxide administration during CPB. Utilizing a novel low-flow then normal-flow CPB strategy, AKI was successfully induced in a subset of animals. Although the study size was limited, the results appear persuasive. Compared with controls, nitric oxide supplementation was associated with decreased postoperative creatinine levels, less histopathologic evidence of moderate/severe AKI, and a trend toward decreased stage 3 AKI. Blood urea nitrogen and cystatin C levels also trended lower at multiple postoperative time points, and may have reached significance in a higher-powered study. The authors conclude that this study corroborates other clinical reports that nitric oxide therapy during CPB may be associated with improved kidney function.

Thus far, the results in human clinical studies have been mixed, with the more favorable outcomes shown in adults. In 1 randomized controlled trial of 96 adults undergoing elective cardiac surgery, nitric oxide administration during CPB was associated with decreased AKI. In another randomized controlled trial of 244 adults undergoing valve replacement surgery, nitric oxide supplementation during CPB and by inhalation for an additional 24 hours decreased the incidence of AKI, transition to stage 3 chronic kidney disease, and major adverse kidney events. Currently, similar positive studies in children are lacking. In a retrospective cohort study of 591 children younger than age 18 years, nitric oxide during CPB was not associated with differences in postoperative creatinine levels or incidence of AKI. Likewise, in the multicenter NITRIC (Nitric Oxide During Cardiopulmonary Bypass to Improve Recovery in Infants With Congenital Heart Defects) randomized control trial involving 1371 children younger than age 2 years, nitric oxide during CPB was also not associated with differences in postoperative creatinine levels or rates of AKI. Although speculative, these conflicting findings in adults and children may be potentially attributable to differences in the underlying health of the vascular endothelium. In response to hemolysis and nitric oxide depletion, a healthy endothelium can compensate through increased nitric oxide production. On the other hand, dysfunctional endothelium is unable to mount an appropriate response and the endogenous pool of nitric oxide is compromised. Adult patients

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Disclosures: The author reported no conflicts of interest.

The Journal policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

Received for publication April 12, 2023; accepted for publication April 13, 2023.
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J Thorac Cardiovasc Surg 2023;165:1-2
0022-5223/$36.00
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https://doi.org/10.1016/j.jtcvs.2023.04.043
undergoing cardiac surgery may have worse baseline endothelium function due to the common risk factors of atherosclerosis, peripheral vascular disease, obesity, and diabetes. Consequently, these patients may experience a greater relative benefit from nitric oxide supplementation. Although it remains to be seen whether or not intraoperative nitric oxide supplementation will gain traction in the prevention of CPB-associated AKI in either population, the results of this ovine study are encouraging and argue that further investigation is warranted.

References