Commentary: Just say NO? Does nitric oxide improve myocardial protection during cardiac surgery?

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Disclosures: Authors have nothing to disclose with regard to commercial support.

Received for publication Oct 10, 2018; accepted for publication Oct 10, 2018; available ahead of print Nov 20, 2018.

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J Thorac Cardiovasc Surg 2019;157:2337-8

0022-5223/\$36.00

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<https://doi.org/10.1016/j.jtcvs.2018.10.044>

Ischemia-reperfusion injury during cardiopulmonary bypass (CPB) is inevitable, and the quest to ameliorate this injury has been pursued for decades. In their study in this issue of the *Journal*, Kamenshchikov and colleagues¹ have taken on this challenge, hypothesizing that nitric oxide (NO) in the cardiopulmonary bypass circuit will reduce myocardial injury during coronary artery bypass grafting (CABG) surgery. The salutary effects of NO have been the subject of intense investigation, which indeed culminated with the Nobel Prize in Medicine in 1998.² For adult cardiac surgery, the use of NO and phosphodiesterase inhibitors has primarily affected the management of pulmonary hypertension. NO, however, has multiple potential effects on cardiac myocytes, including enhancement of myocyte relaxation and inhibition of myocardial oxygen consumption.³ This is also precisely the goal of myocardial protection and cardioplegia during cardiac surgery. The use of NO during CPB has previously been evaluated in congenital heart surgery has been shown to reduce myocardial injury and improve outcomes.^{4,5}

Kamenshchikov and colleagues¹ present a single-institution prospective study of 60 CABG patients randomly allocated to receive 40 ppm of NO versus control. Myocardial injury was assessed with biomarkers (cardiac troponin I, creatine kinase isoenzyme MB) at 6 and 24 hours postoperatively. They found that both cardiac troponin I and creatine kinase isoenzyme MB were lower in the NO-treated group. In addition, vasoactive inotropic support scores were calculated within the first 48 hours of surgery. They found that NO-treated patients had decreased vasoactive inotrope requirements relative to controls. There are 3 main points that bear mentioning when considering this study. First, this study is limited by a small cohort of low-risk patients undergoing CABG, making it difficult to draw any strong conclusions. It is unclear whether CABG represents the best patient cohort to evaluate the potential benefit of NO. Overall, CABG has become a low-risk

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Central Message

Nitric oxide plays a critical role in myocardial ischemia-reperfusion injury and may further augment myocardial protection strategies related to cardiopulmonary bypass.

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cardiac surgery operation, especially for patients with normal ventricular function undergoing an elective operation. A more salient clinical benefit might be detected in patients with ventricular dysfunction, recent myocardial infarction, incomplete revascularization, or more complex operations. Second, it is unclear whether cardiac injury biomarkers are independently prognostic of clinical outcomes. Beller and colleagues⁶ found that peak troponin does not influence CABG outcomes after myocardial infarction. Furthermore, there are many randomized control trials demonstrating decreased biomarkers of injury in off-pump CABG, but little change in outcome. Third, the systemic effects of NO should be considered. These systemic effects may prove to have a benefit independent of myocardial injury. In a study by Cecchia and colleagues⁴ in pediatric patients undergoing tetralogy of Fallot repair, the addition of NO to the CPB circuit led to improved fluid balance.⁴ Furthermore, in a study by Lei and colleagues,⁷ the addition of NO to the CPB circuit in patients undergoing mitral valve replacement led to less acute kidney injury.⁷ These findings suggest that systemic effects of NO may be beneficial.

This pilot study shows that administration of NO during CPB is safe, feasible, and economical. Further randomized trials and larger investigational studies are needed. Future studies should be performed in a cohort of higher risk patients, with outcomes that assess myocardial protection and systemic benefits.

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