Nitric Oxide Treatment for Lungs and Beyond

Novel Insights from Recent Literature

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Recommended Reading from the Massachusetts General Hospital Department of Anesthesia, Critical Care, and Pain Medicine Fellows; Lorenzo Berra, M.D., Medical Director for Research in Surgical Intensive Care and Faculty Mentor

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Nagasaka Y, *et al.* Pharmacological Preconditioning with Inhaled Nitric Oxide (NO): Organ-Specific Differences in the Lifetime of Blood and Tissue NO Metabolites. *Nitric Oxide* (1)

Reviewed by Francesco Zadek

Nowadays, inhaled nitric oxide (iNO) is commonly used off-label as a pulmonary vasodilator for treatment of pulmonary hypertension in adults (2). Although devoid of systemic hemodynamic effects, iNO has recently been shown to have protective properties in the context of ischemia–reperfusion injury (IRI) of the brain, heart, and kidneys (3–9). These beneficial effects could be mediated by circulating NO metabolites such as nitrite, nitrate, *S*-nitrosothiol (RSNO), *N*-nitrosamine, nitrosylheme (NO-heme) (10), and nitrosylated plasma proteins.

Recently, Nagasaka and colleagues assessed the pharmacokinetics of NO metabolites in peripheral organs after iNO, and the preconditioning effects of iNO and NO metabolites, in a murine model of myocardial IRI (1). The study consisted of two sets of experiments. In the first study, mice were randomized to breathe either 80 ppm of iNO or air for 1 hour. Animals were killed at different time points after the cessation of gas administration to characterize the decay of the concentrations of different NO metabolites within peripheral organs. NO metabolite concentrations were obtained from samples of blood, urine, and pathologic specimens (kidney, liver, lung, brain, and heart tissue).

In the second study, mice were randomized to breathe either 80 ppm of iNO or air for 1 hour. A model IRI was obtained by closing the left anterior descending coronary artery for 1 hour with a surgical knot. Twenty-four hours after the reperfusion, the mice were killed, and the hearts were inspected to determine the ratio of the areas at risk for IRI to the infarcted area.

No changes in plasma nitrite concentrations were reported. Nitrate, RSNO, *N*-nitrosamine, and NO-heme increased in all organs assessed, with the exception of the brain. The elevated NO metabolites lasted longer in the tissue than in the plasma and in the red blood cells, and decay profiles were metabolite organ specific.

The mice that received iNO showed an infarcted area/area at risk ratio which was decreased by 30%, confirming the protective effect of NO against IRI observed in previous studies (3, 8, 9, 11). In the heart, the only NO metabolites that increased were RSNO and NO-heme. The authors concluded that the storage of long-lasting NO metabolites within myocardial tissue allowed local release of NO during the vascular occlusion, activating protective antiinflammatory and antioxidant pathways. ■

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Janssens SP, *et al.*; NOMI Investigators. Nitric Oxide for Inhalation in ST-Elevation Myocardial Infarction (NOMI): A Multicentre, Double-Blind, Randomized Controlled Trial. *Eur Heart J* (12)

Reviewed by Stefano Spina

Janssens and colleagues (12) recently conducted a randomized, double-blind, multicenter phase II study to investigate whether the off-label use of iNO reduces IRI (13) in patients with ST-elevation myocardial infarction after successful percutaneous coronary intervention. The authors randomized 250 adult patients to receive either 80 ppm of iNO ($n = 123$) or a placebo ($n = 127$) through a facemask for 4 hours upon arrival in the catheterization laboratory. The primary endpoint was the difference in infarct size between the iNO and control groups. Infarct size was defined as a percentage of affected tissue relative to the left ventricular mass at 48–72 hours. A subgroup analysis was also performed to explore the possible interaction effect of intraprocedural use of nitroglycerin in patients receiving iNO.

The authors reported that iNO did not decrease infarct size/left ventricular mass, the primary endpoint, at 48–72 hours ($18.0 \pm 13.5\%$ vs. $19.4 \pm 15.4\%$, iNO vs. placebo, respectively; $P = 0.427$). In the subgroup analysis assessing the effects of nitroglycerin administration during coronary angioplasty, the authors found a statistically significant benefit in both primary and secondary endpoints only in nitroglycerin-naive patients receiving iNO and no benefit in patients receiving a combination of iNO and nitroglycerin. Among other secondary endpoints was measurement of left ventricular dimensions: patients who were enrolled in the iNO group had smaller left ventricular dimensions ($P = 0.048$) at 4 months than patients receiving the placebo.

This study provides insights into the cardioprotective mechanisms of NO. Although NO has a very short half-life in the blood, NO metabolites have the ability to transfer NO molecules from the lungs to peripheral tissues, where their benefits may be exerted (1). The results of this trial suggest that additional iNO might not add beneficial effects already conferred by nitroglycerin, an NO donor. It is unlikely that a higher dose of NO could lead to different results (11), but it is possible that earlier administration of the gas during the ischemic phase may play an important role in protecting the myocardium from IRI (9).

In a select group of nitroglycerin-naive patients, iNO seemed to reduce infarct size, revealing an extrapulmonary protective effect, as previously shown in animals (14). On the basis of these results, it can also be hypothesized that iNO could be used instead of nitroglycerin when a patient's hemodynamics preclude the use of nitroglycerin. For safety and when applicable, NO gas in the environment should be monitored to avoid unnecessary exposure of personnel (or patients not involved with the treatment). ■

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James C, *et al.* Nitric Oxide Administration during Paediatric Cardiopulmonary Bypass: A Randomised Controlled Trial. *Intensive Care Med* (15)

Reviewed by Jie Hu

James and colleagues investigated the benefits of the off-label use of NO delivery via the cardiopulmonary bypass (CPB) oxygenator in children with congenital heart disease undergoing cardiac surgery (15). Their data showed that 101 children who received 20 ppm of NO developed low cardiac output syndrome less frequently (15% vs. 31%; $P = 0.007$) than the 97 children who did not receive NO. This effect was most significant in children younger than 6 weeks of age (20% vs. 52%; $P = 0.012$) and in those aged 6 weeks to 2 years (6% vs. 24%; $P = 0.026$). In addition, the latter group had a significantly reduced ICU length of stay (43 vs. 84 h; $P = 0.031$). Extracorporeal membrane oxygenation was used less often in the NO group (1% vs. 8%; $P = 0.014$).

To interpret the results of this study, one should consider the following limitations: first, 40% of eligible patients were not included (198 of 490); second, the perfusionist was not blinded to group allocation for safety reasons; and third, this was a single-center investigation. Local practices related to anesthesia, CPB, surgery, extracorporeal membrane oxygenation deployment, and postoperative care might have influenced outcomes, limiting the general applicability of the study.

The authors suggested possible beneficial mechanisms of breathing NO in pediatric patients undergoing cardiac surgery. First, prolonged procedures requiring CPB are associated with progressively higher degrees of hemolysis (16), causing the release of free hemoglobin (17) and increase of NO inhibitor asymmetric dimethylarginine (18). The dioxygenation reaction with the free hemoglobin together with the inhibition of the endothelial NO synthetase causes vascular NO depletion, leading to endothelial dysfunction and vasoconstriction (19, 20). Supplementing NO into the CPB circuit could reduce NO consumption (21), possibly decreasing postoperative systemic and pulmonary vascular resistance

and thus improving ventriculoarterial coupling, cardiac output, and organ perfusion (22). Second, CPB could induce systemic inflammation due to IRI, which could contribute to myocardial dysfunction (23) and to further decrease in endogenous NO production (24, 25). In this setting, iNO could exert immune modulation and limit myocardial dysfunction (4).

This study adds further evidence to the potential cardioprotective properties of supplemental NO gas during cardiac surgery (15, 26–28). Multicenter, definitive phase III trials should test whether supplementation of NO improves survival in pediatric and adult patients undergoing CPB surgery. ■

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Conclusions

These three studies lead to the following considerations. First, plasma and red blood cells are a systemic circulating storage of NO metabolites that deliver and receive NO species to and from several organs. Second, the preconditioning effect in the heart is carried by stored RSNO and NO-heme, long-lasting NO metabolites acting as NO donors. Thus, to maximize cardioprotection, iNO must be delivered before the start of an ischemic insult to increase concentration of RSNO and NO-heme within cardiac tissue. Theoretically, iNO targets and NO metabolites might exploit the preconditioning effects by enhancing either cyclic guanosine monophosphate–dependent (29) or cyclic guanosine monophosphate–independent pathways (30). Future trials might consider whether inhalation of NO has similar protective properties for other systemic organs. ■

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