See Article page 841.

Commentary: Say yes to NO!

Alberto Benazzo, MD, and
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Ex vivo lung perfusion (EVLP) has become an indispensable safety net in lung transplantation, as it allows to evaluate marginal donor lungs for an extended period of time before accepting them for transplantation. However, the potential of EVLP goes far beyond a “simple” organ-evaluation tool. It also represents a platform to recondition damaged donor lungs by targeted therapeutic interventions. The use of high-dose antibiotics during EVLP has previously been shown to significantly reduce the microbial load¹; however, its clinical applicability is limited by the varying microbial spectrum of donor lungs and by the difficulty to target multidrug-resistant bacteria.

In the article “Pulmonary Safety of Continuous 12-hour Delivery of Antimicrobial Doses of Inhaled Nitric Oxide During Ex Vivo Lung Perfusion,” Michaelsen and colleagues² tested the therapeutic potential of high-dose inhaled nitric oxide (iNO) during EVLP. In a first set of in vitro experiments, the antibacterial activity of high-dose iNO was determined; subsequently, its therapeutic safety was investigated in a pig model of EVLP. The authors showed that iNO could efficiently reduce bacterial growth, both in solid and liquid culture assays, and a continuous delivery of iNO over a 12-hour EVLP run did not induce pulmonary inflammation or impair graft function.

Today, low-dose iNO (<20 ppm) is routinely used in a variety of disorders, including acute respiratory distress syndrome,³ decompensated pulmonary hypertension,⁴ and pulmonary hypertension of the newborn.⁵ By activating

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CENTRAL MESSAGE

Adding high-dose inhaled nitric oxide to ex vivo lung perfusion is a promising new approach to reduce the microbial load in donor lungs.

guanylyl cyclase in the pulmonary vascularity, iNO mediates vasodilation, reduces pulmonary vascular resistance, and thereby improves a ventilation–perfusion mismatch. Moreover, it has been shown that iNO exerts anti-inflammatory and antiapoptotic effects.^{6,7} In the current study of the Toronto EVLP research group, iNO-treated lungs showed a trend toward an improved dynamic and static compliance as well as a reduction in pulmonary vascular resistance. Although this study primarily aimed to evaluate antimicrobial effects of iNO, these measurements point toward an additive beneficial effect of high-dose iNO during EVLP.

Once more, the current work highlights the versatility of the Toronto EVLP platform and the great therapeutic potential that comes with it. Several examples can be found in the literature, ie, administration of fibrinolytic agents to dissolve pulmonary thromboemboli,⁸ the treatment of donor lungs with rituximab to deplete Epstein–Barr virus-bearing B cells,⁹ and the application of light therapy to inactivate circulating virus particles.¹⁰ The combination of high-dose iNO and EVLP constitutes a significant step toward a universal organ repair machine that can provide a variety of treatments tailored to the needs of each allograft.

In conclusion, high-dose iNO represents another part in the fascinating puzzle of ex vivo organ manipulation. In near future, a large proportion of reversible donor lung pathologies will be correctable by EVLP. Not all proposed therapeutic adjuncts of EVLP will find their way into the

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clinical practice, but the simplicity and the therapeutic potential of nitric oxide suggest a “yes” for NO.

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See Article page 841.

Commentary: To use or not to use...Is NO the answer?

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Normothermic ex vivo lung perfusion (EVLP) holds great promise as a platform to recondition donor lungs of unacceptable quality to make them suitable for transplantation. Experimental studies using EVLP as a platform for therapeutic interventions have included strategies to treat aspiration and hepatitis C, among others.^{1,2} If successful and adopted broadly, such strategies could significantly diminish the persistent shortfall of suitable lungs available for transplantation.

In this issue of the *Journal*, Michaelsen and colleagues³ present a study examining the feasibility and safety of

CENTRAL MESSAGE

Administration of continuous high-dose (200 ppm) inhaled nitric oxide during 12-hour porcine ex vivo lung perfusion (EVLP) is safe and may be a novel treatment for lung infection during EVLP.

high-dose inhaled nitric oxide (iNO) as potential antimicrobial treatment during porcine lung EVLP. Lung infection is a common reason for declining donor lungs and can result in poor post-transplant outcomes.^{4,5} Several studies have used high-dose, broad-spectrum antibiotics to treat infected human or pig lungs over 3 to 12 hours of EVLP with good results (reduction in bacterial counts and improved lung function).⁶⁻⁸ With such promising studies, why consider the use of iNO?

At high doses, NO has broad-spectrum antimicrobial activity.⁹ Recent clinical studies have used high-dose iNO to successfully treat antibiotic-resistant infections in patients

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