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 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.3,5 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).3,9 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

References

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with cystic fibrosis.\textsuperscript{10,11} Due to the time- and dose-dependent oxidation of hemoglobin to methemoglobin, as well the potential production of the toxic molecules nitrogen dioxide and peroxynitrite in the presence of oxygen, these studies used intermittent (3-5 times/day), short-duration (30 minutes) exposure to high-dose (160 ppm) iNO. Michaelsen and colleagues postulated that high-dose iNO could be used in acellular EVLP to treat infection while avoiding the in vivo toxicities. This EVLP strategy could be more efficacious than antibiotics, avoid potential induction of antimicrobial resistance with antibiotic use, and avoid the conundrum of selecting antibiotics without knowing the sensitivity profile of the microbial flora.

Using normal pig lungs, Michaelsen and colleagues demonstrated that exposure to continuous iNO at 200 ppm during 12 hours of acellular EVLP did not negatively impact physiological parameters and further demonstrated that there was no difference in histology or levels of proinflammatory cytokines compared with nontreated EVLP controls. Using ventilation with an inspired oxygen fraction of 0.21, and with absence of hemoglobin in acellular EVLP, nitrogen dioxide levels were low, as were perfusate methemoglobin levels.

As an initial safety and feasibility study, Michaelsen and colleagues are to be congratulated for their novel and important work. Many questions remain, however. The major limitation of the study, as noted by the authors, is that although they propose to treat lung infection, they did not use infected lungs in their study, as the development of a porcine lung infection model is ongoing. This leaves unanswered questions, such as the ability of an airway-based treatment to reach areas of consolidated lung, the potential synergy of iNO with antibiotics, and the necessary time of iNO exposure (most clinical EVLP is limited to 3-6 hours). Will 3-6 hours be sufficient time for an inhaled therapy? Based on the trials in cystic fibrosis, it might, but whether NO is the answer will have to await evaluation in infection models.

References


