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Nasally Inhaled Nitric Oxide for Sudden Right-sided Heart Failure in the Intensive Care Unit: NO time like the Present

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Inhaled nitric oxide (iNO) is an exogenously administered pulmonary vasodilator (iPVD), which serves to replicate the actions of endogenously derived vascular endothelial nitric oxide. In this regard, iNO induces pulmonary vascular smooth muscle relaxation by activating soluble guanyl cyclase to increase cyclic guanosine monophosphate (cGMP) generation and downstream myosin light chain dephosphorylation with reductions in intracellular calcium.[1] Inhaled NO is approved by the Food and Drug Administration for use in persistent pulmonary hypertension of the newborn, but is commonly used “off-label” in critically-ill adult patients worldwide to reduce increased pulmonary vascular resistance (PVR) for afterload reduction during acute right-sided heart failure (RHF)[2] or to treat hypoxic pulmonary vasoconstriction.[2,3] These indications are most common in the subset of adult patients undergoing cardiovascular or thoracic surgery. The agent is initiated either in the operating room or in the intensive care unit (ICU) before or after surgery. Inhaled NO has become the mainstay of iPVD therapy for these critically ill patients despite sparse evidence for improved clinical outcomes after use.[4] Furthermore, iNO is often administered while RHF patients are tracheally intubated on mechanical ventilation, when gas exchange is better controlled in the struggling, critically ill patient. Although iNO may be prescribed by the nasal route during spontaneous breathing, the efficacy and delivery of iNO to the precapillary arterioles or alveolocapillary networks for vascular relaxation or improved ventilation-to-perfusion matching[5,6] is largely unknown.

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In this issue of the Journal, Tremblay et al. describe the noninvasive initiation of iNO in 18 spontaneously ventilating ICU patients with natural airways in order to demonstrate reductions in right-sided cardiac filling pressures and improvements in cardiac output during acute RHF.[7] Each patient in this retrospective cohort served as their own control and hemodynamic comparisons were made within 1 hour before and 1 hour after iNO initiation at a median rate of 20 parts per million. Twelve patients were started on nasal iNO after they were extubated following cardiovascular surgery and 6 patients were administered nasal iNO for non-operative circumstances. Upon analysis, iNO reduced PVR from 2.7 to 2.0 Wood units ($N=7$, $p<0.001$) and cardiac index improved from 2.0 to 2.6 L/min/m^2 ($N=9$, $p=0.004$).[7] In the remainder of patients, changes in pulmonary or central venous pressures illustrated statistically significant reductions after nasal iNO initiation. Furthermore, about 28% of patients received iNO via high-flow nasal cannula, in which oxygen delivery and amelioration of hypoxic vasoconstriction could confound the improvement in PVR derived from iNO. Incidentally, although mean pulmonary arterial pressures (mPAP) decreased from 28.4 to 25.3 mm Hg (n=8, 95% Confidence Interval [0.7 to 5.6], $p=0.01$), mPAP $\geq$ 25 mm Hg is still considered diagnostic for PH.[8] Interestingly, these relatively minor improvements in PVR were associated with significant improvements in cardiac index and central venous pressure, with stable inotropic support. This finding may suggest that iNO significantly improved right ventricular-pulmonary arterial (RV-PA) coupling out of proportion to clinically quantifiable changes in pulmonary vasodilation in these patients. Inotropic properties of epoprostenol have been the topic of much debate due to the mechanism of the prostaglandin agonist, which promotes cyclic adenosine monophosphate generation in RV myocardium.[9] This explanation cannot be readily attributed to iNO given the different mechanisms of action. Nevertheless, additional studies of adequate sample size will be required to accurately study this relationship. Notably, the direction of “crossover” from no iPVD therapy to iNO use was unidirectional and data were not presented in patients after iNO had been discontinued. Data measurement occurred across a two-hour period and changes in inotropes, vasopressors, or inodilators were carefully compared across this time period and found to be statistically insignificant ($p \geq 0.05$). Although collecting such data was thorough and thoughtful, interpreting such results pose great challenge given such a small sample size and a complex clinical disease.

Unidirectional crossover designed studies pose a common dilemma in clinical research because the time-period associated with data analysis, which may include changes in clinical status, is compensated for by utilizing an often narrow duration to compare data for a paired analysis.[10] If the temporal window is expanded, this analysis may adjust for time in order to limit “carryover” effects from the nontreatment period, but statistical adjustment may make incorrect clinical assumptions about this time-period. Such assumptions could be misleading especially in the complex ICU environment. Prospectively designed crossover studies may allow for randomizing the direction of crossover, i.e., half the cohort begins with the treatment and crosses over to no treatment whereas the other half begins with no treatment and crosses over to the treatment arm. Conversely, collecting data after the treatment is completed, i.e., crossover from iNO to no iNO therapy, in a retrospective study, may strengthen the intended message.

Regardless of the design, small sample size, and preliminary nature, the study by Tremblay et al., provides early evidence for other potential routes of iNO administration during the management of RHF in perioperative and intensive care settings. The common presence of mechanical ventilation and iPVD administration has coexisted in order to control gas exchange, allow patient rest, and avoid cardiopulmonary collapse. Over time, these associated therapies have led to the belief that invasive ventilation should be the "gold standard" method for reliable iPVD pulmonary delivery. However, the absence of evidence is not the evidence of absence, and despite fixed beliefs passed down from spoken perioperative and intensive care dogma, nasal iNO is commonly used for pulmonary vasoreactivity testing and diagnosis of the vasoresponder phenotype in nonoperative patients with pulmonary arterial hypertension.[11] Therefore, the clinical use of nasal iNO is not necessarily novel. Importantly, nasal delivery of iNO or other iPVD agents may occur without high-level resource utilization, despite a relatively high-cost burden of iNO compared with other iPVD agents. In fact, it would be novel to determine if nasal iPVD reduces the incidence of cardiopulmonary failure, endotracheal intubation, and mechanical circulatory support in the RHF patient. Nevertheless, several challenges remain in negotiating the effective delivery of nasal iNO therapy in these critically ill patients with acute RHF, where nasal iPVD delivery may provide adequate benefits while avoiding the noteworthy risks of general anesthesia and endotracheal intubation.

First, the lung dynamics related to spontaneous and controlled ventilation are not yet reconciled with regards to iPVD delivery. In mechanically ventilated patients who are synchronous and positively ventilated, minute ventilation remains consistent and iPVD delivery is presumed to be similar between mechanically delivered breaths. On the other hand, ventilator adjustments to improve gas exchange may alter tidal volume, positive-end expiratory pressure, and bias gas flow rate, which can potentially affect iPVD delivery per unit of time. Further, mechanically-controlled ventilation is also thought to be "non-physiologic," leading to shunting across alveolar capillaries that may otherwise contribute to gas-exchange in certain locations or dead-space ventilation without viable capillary flow at other regions, and this imbalance may further increase PVR. Second, iNO rapidly reacts with oxyhemoglobin and deoxyhemoglobin to form nitrate and nitrosylated hemoglobin, respectively; therefore, performing pharmacokinetic and pharmacodynamics studies in this population will require a thoughtful and elegant approach. Interestingly, this pulmonary "sink" related to iNO administration is an important reason for its use, since changes in systemic vascular resistance are postulated to rarely occur. Third, the efficacy of iNO, or other iPVD agents, in reducing PVR and improving RV systolic function in severe PH and overt RHF has not been evaluated in a dose-response fashion in critically ill adult patients.

Sudden-onset RHF related to elevated PVR has high potential for cardiac arrest during induction of general anesthesia to facilitate endotracheal intubation, and evidence which supports the noninvasive nasal administration of iNO to reduce PVR, avoid intubation, and improve right ventricular contractility, allows the practitioner to consider another option for route of delivery. Nevertheless, the inertia of ICU protocols and algorithms, coupled with the growing patient disease severity, may further complicate a simple, binary decision to use or not use nasal iNO. What is sorely needed in this area is randomized and blinded data regarding the efficacy of iPVD therapy in right heart failure. Currently, we are

conducting a randomized clinical trial of adult patients undergoing left ventricular assist device (LVAD) placement, orthotopic heart transplantation, or lung transplantation, who are receiving iPVD therapy in blinded fashion with either iNO or aerosolized epoprostenol (link: https://clinicaltrials.gov/ct2/show/NCT03081052). We are primarily assessing the incidence of RHF after LVAD placement or heart transplantation, and the incidence of severe primary graft dysfunction after lung transplantation. Trial participants in both iPVD groups are initially administered the randomized/blinded agent through the endotracheal tube while on mechanical ventilation, and the same agent is administered by nasal route in the ICU after postoperative extubation and ventilator liberation. This trial is not specifically evaluating the route of delivery between the two groups but the findings in Tremblay et al.[7] offer important early evidence for the efficacy of nasal iNO (and perhaps other nasally administered iPVD agents) in this critically ill patient population. Additional prospective studies are needed to evaluate differences in the route of administration and the dose-dependent response to these inhaled agents.

Disclosure:

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