Inhaled Nitric Oxide for Fibrotic Interstitial Lung Disease: A Step Forward

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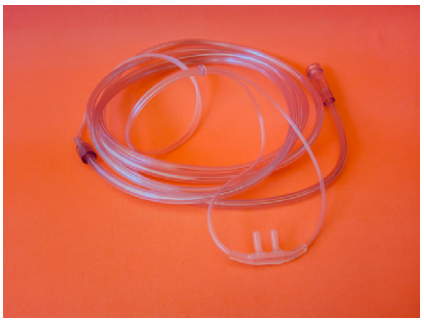

Nitric oxide (NO) is one of the oldest gases on earth and has existed since the prebiotic atmosphere. Although the medical use of NO was first reported in 1867 to treat angina pectoris, its role as an endothelial-derived vasodilator factor was not recognized until 1987 (1). The therapeutic potential of inhaled NO (iNO) was subsequently proposed in the early 1990s (2, 3). iNO provides local pulmonary vasodilation with limited systemic effects owing to its short half-life in the bloodstream resulting from its rapid inactivation by hemoglobin.

In 1999, the Food and Drug Administration approved iNO as a therapeutic option in newborns with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension (PH) for improving oxygenation and reducing the need for extracorporeal membrane oxygenation (4). In adults, iNO is used for treating patients with acute respiratory distress syndrome in intensive care units. Novel delivery systems and user-friendly NO generators with improved portability have been developed in recent years, offering the potential of extending its therapeutic use into the community (5).

In this issue of *AnnalsATS*, King and colleagues (pp. 594–602) report the results of a phase 2 randomized, double-blinded, placebo-controlled trial of 4-month pulsed iNO at 45 μg/kg ideal body weight/hour (iNO45) delivered via the INOpulse (a cylinder-based delivery system) in 44 patients with fibrotic interstitial lung disease (ILD) on home oxygen therapy (6). Their previous proof-of-concept study found that the use of pulsed iNO at 30 μg/kg ideal body weight/hour (iNO30) for 2 months was safe and improved moderate to vigorous physical activity levels (7). Consistently, this longer-term use of a higher dose of pulsed iNO was safe without serious adverse effects. Furthermore, compared with the placebo group, the iNO45 group had better preserved moderate to vigorous physical activity levels measured by actigraphy and dyspnea control measured by the University of California San Diego–Shortness of Breath Questionnaire, with the mean differences exceeding clinically meaningful thresholds. Similar results of physical activity levels were observed when stratified by the probability of PH. In addition, there were between-group differences for St. George's Respiratory Questionnaire activity and impact domain scores, as well as the total scores, with superior quality of life in the iNO45 group. These early but impressive findings substantiate the need for a more robust and definitive trial of iNO in patients with fibrotic ILD to inform clinical practice, which is currently underway (the REBUILD A Randomized, Double-Blind, Placebo-Controlled Dose Escalation and Verification Clinical Study to Assess the Safety and Efficacy of Pulsed Inhaled Nitric Oxide [iNO] in Subjects at Risk of Pulmonary Hypertension Associated With Pulmonary Fibrosis on Long Term Oxygen Therapy [Part 1 and Part 2] trial; ClinicalTrials.gov Identifier: NCT03267108).

Although the exact mechanisms are yet to be fully elucidated, PH and hypoxemia likely have a bidirectional relationship in fibrotic ILD, with one aggravating or predisposing to the other (8, 9). Notably, both PH and hypoxemia share common detrimental effects on functional capacity, quality of life, and survival in this population, with limited proven effective therapies (10, 11). Although oxygen therapy is commonly prescribed for these patients, currently available portable oxygen delivery devices are often inadequate to meet the high oxygen demands frequently encountered among patients with a significant degree of hypoxemia, particularly during exertion (12). The selective pulmonary vasodilatory effects in well-ventilated lung units, exerted by appropriate dosing of pulsed iNO, can improve ventilation–perfusion mismatch and transpulmonary oxygenation, without increasing intrapulmonary shunting. This has been shown using computed tomography–based functional respiratory imaging in patients with chronic obstructive pulmonary disease (COPD) and concomitant PH breathing pulsed iNO and oxygen (13). In a 3-month trial of patients with PH secondary to COPD requiring long-term oxygen therapy, the addition of pulsed iNO improved pulmonary vascular hemodynamics and cardiac output without affecting gas exchange and systemic

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Table 1. Types of NO delivery systems

Types	Descriptions
Cylinder-based systems	Pressurized cylinders of different concentrations of NO buffered with an inert gas
Chemical-generated NO systems	Use of cartridges with specific chemicals for generating NO
Electricity-generated NO systems	Use of pulsed electrical discharge for generating NO from the air or a gas mixture
Nanoparticle NO technology	NO- or inactive NO precursor–containing nanoparticles with controlled release of NO when applied to the target tissue
NO-releasing solutions	NO-releasing solutions under specific conditions, which have been designed for topical use for infection control

Definition of abbreviation: NO = nitric oxide.

hemodynamics (14) Pulmonary vascular hemodynamics were not included as outcomes in the current study; however, one would assume that similar effects of pulsed iNO would likely be observed in patients with fibrotic ILD.

King and colleagues are to be commended for the rigor and careful attention to detail applied in their preliminary investigation of the therapeutic effects of ambulatory pulse iNO in fibrotic ILD. Amid a series of early-phase studies being conducted for the evaluation of safety, the study design of this clinical trial stands out and sets the stage for the upcoming phase 3 clinical trial. The authors selected clinical endpoints focused on functional status, an outcome that is of great relevance to patients. Functional status is increasingly emphasized as a key outcome in clinical trials of patients with fibrotic ILD, as it represents a complex multidimensional construct of symptom burden and intervention received. Multiple tests are available for measuring functional status, either subjectively using self-administered questionnaires or objectively using clinical exercise tests and physical activity monitors. In comparison with clinical exercise tests that evaluate patients' functional status in a controlled environment cross-sectionally, physical activity monitors assess habitual patterns and levels of patients' functional status over longer time periods. Findings from the early-phase studies of iNO prompted the authors to revise the primary efficacy outcome measure of the planned phase 3 clinical trial from the change in 6-minute-walk distance to the change in moderate to vigorous physical activity levels. Identifying the limitation of a short run-in period with inadequate actigraphy data for baseline assessments allowed for adjustment of the clinical trial design to minimize the chance of unanticipated analytical issues.

Despite the encouraging results shown in this phase 2 exploratory study of pulsed iNO, we should refrain from the tendency to get overly excited while we await the evaluation of iNO in phase 3 clinical trials. In patients with pulmonary arterial hypertension, a phase 3 clinical trial of pulsed iNO was terminated early because of the lack of clinical benefit after the interim analysis (15). At this point, there are seemingly more questions than answers. The optimal dose of iNO at which maximal therapeutic value is attained without toxicity remains yet to be determined. Also, whether this effective dose varies across individuals requiring dose titration, and by how much, is unknown. Furthermore, differences in the actual usage of pulsed iNO across patients and their perspectives of frequent ambulatory use of two inhalational support devices have not been evaluated. Lessons learned from studies of ambulatory oxygen therapy in fibrotic ILD suggest that compliance and acceptability of device interventions can be affected by the associated psychosocial burden and physical challenges linked to these devices (16, 17).

With the current rapid pace of technological advances, improved iNO delivery systems that may provide an alternative to the presently available cylinder-based systems (Table 1) are in development. These hold great promise for a better quality of life and could be more suitable for day-to-day use as self-sustaining sources. Nevertheless, as we search for interventions to manage functional capacity and symptoms in patients with fibrotic ILD, this study offers an exciting motivational spark for further evaluation of pulsed iNO as a potential therapeutic option—one for which we have long been hopeful. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Leveraging Family Experience to Improve Their Engagement in the Intensive Care Unit

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Since the emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), patients hospitalized with coronavirus disease (COVID-19) have been cared for in hospitals that enacted new, and often restrictive, visitor policies (1–3). These policies arose out of fear regarding the transmissibility of SARS-CoV-2, the uncertainty in the effectiveness of personal protective equipment at preventing transmission, and limited personal protective equipment supply (3). It was hoped that restricting visitation would limit the spread of SARS-CoV-2 and protect hospital staff who were desperately needed as the pandemic took hold. Though data are limited, it appears that visitor restrictions were nearly universal, and in the majority of hospitals no visitors were permitted in the absence of extraordinary circumstance, such as end-of-life events (1). These policies may have had their most severe consequences in intensive care units (ICUs), where the acuity of illness and the urgency of decision making for patients and their surrogates is most immediate.

Representing the F, for Family Engagement, in the Society of Critical Care Medicine's ABCDEF bundle to promote ICU liberation and survivorship, family engagement for patients with critical illness is a key element of evidence-based critical care medicine (4). Family engagement can decrease the risk of delirium, improve collaborative decision making, and reduce patient suffering. In addition, family members of critically ill patients may themselves experience long-term psychological effects, including depression, post-traumatic stress disorder (PTSD), and complicated grief (5). Fortunately, family engagement during a patient's ICU stay can lessen the morbidity of critical illness for both patients and their families (6). Specific to the COVID-19 pandemic, the *lack* of family presence was one of only two modifiable delirium risk factors found in a large international study of critically ill patients with COVID-19 (7). Evidence also suggests that visitor restriction policies related to COVID-19 delayed important goals of care decisions and may have prolonged the suffering of patients in the ICU who ultimately died (8). The absence of family at the bedside may have complex effects on the experiences of ICU clinicians (9). However, difficulties with communication, loss of the humanizing presence of families, and witnessing patient deaths without family present may increase the burnout and moral distress that is now endemic among those caring for patients in the ICU during the COVID-19 pandemic (9, 10).

With the evolution of new SARS-CoV-2 variants and incomplete vaccination coverage, visitor restriction policies will likely continue in some form. As we see this happen, visitation policies should be designed to minimize the negative impact that visitor restrictions are known to have on

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