Inhaled Pulmonary Vasodilators in the Neonatal and Pediatric ICU

Brian K Walsh

Inhaled pulmonary vasodilators are a powerful tool in the arsenal of therapies designed to treat pulmonary hypertension in pediatrics. Yet only 1 inhaled vasodilator, inhaled nitric oxide (INO), has been approved by the Food and Drug Administration for use in neonates > 34 weeks gestational age with persistent pulmonary hypertension of the newborn. Off-label use of inhaled vasodilators is common in the neonatal and pediatric population despite a lack of evidence. Growing focus on providing evidence-based therapies combined with the increasing cost of INO has led to the exploration of other inhaled pulmonary vasoactive agents. Advancements in technology have led to the creation of nitric oxide generation devices that do not require tanks. This review evaluates the current evidence regarding the use of inhaled vasodilators and INO delivery devices in the neonatal and pediatric intensive care population. *Key words: neonates; pediatrics; inhaled vasodilators; nitric oxide; pulmonary hypertension; inhaled prostacyclin.* [Respir Care 2020;65(10):1611–1623.

Introduction

Pulmonary hypertension is found in a variety of critical illnesses within the neonatal and pediatric ICUs and is associated with cardiac, pulmonary, and systemic diseases, from neonates to older children. Inhaled pulmonary vasodilators are a powerful tool in the arsenal of therapies designed to treat pulmonary hypertension in neonatal and pediatric populations. Commonly used agents include inhaled nitric oxide (INO), epoprostenol sodium, iloprost, and treprostinil. Yet only 1 inhaled vasodilator, INO, has been approved by the Food and Drug Administration (FDA) for use in specific critically ill pediatric populations (ie, neonates > 34 weeks gestational age with persistent pulmonary hypertension of the newborn [PPHN]). Although evidence supporting the use of inhaled vasodilators outside their FDA-approved indications of use is limited and controversial, off-label use of inhaled vasodilators is common in the neonatal and pediatric population despite this lack of evidence. The will to provide evidence-based therapies combined with increasing cost of INO (estimated to be, on average, $100–125/h[1-3]) has led to the exploration of other inhaled pulmonary vasoactive agents. Advancements in technology have led to the creation of INO delivery devices that do not require tanks, triggering competition in the marketplace. This review evaluates the current evidence of use of inhaled vasodilators and INO delivery devices in the neonatal and pediatric intensive care population.

Diagnosis

Neonatal

Diagnosis of PPHN is made in neonates most often with echocardiography. Echocardiography is used to look for PPHN when unremitting hypoxemia is unexplained by parenchymal lung disease to exclude structural heart defects and confirm diagnosis of PPHN. Echocardiographic studies can demonstrate flow from right-to-left shunting through the ductus arteriosus or foramen ovale. Additionally, through the use of a continuous Doppler measurement of tricuspid jet, estimations of the right-ventricular systolic pressure can be determined. Using the Bernoulli equation, pulmonary artery systolic pressure can be calculated as peak pressure difference = 4 × [peak tricuspid jet velocity]^2, which will be elevated in neonates with PPHN.[4]

Severity of PPHN is determined by estimating the right-ventricular pressure and the degree of atrial or patent ductus arteriosus shunting.

- Mild to moderate PPHN: right-ventricular pressure is 50–75% of systemic blood pressure
- Moderate to severe PPHN: right-ventricular pressure > 75% systemic blood pressure
- Severe PPHN: right-ventricular pressure > systemic blood pressure
  - Evidence of right-ventricular dysfunction
  - Evidence of biventricular dysfunction representing global insult

Figure 1 demonstrates the observed frequency of PPHN by neonatal diseases.[5]

Pediatrics

Pulmonary hypertension in children is defined as a mean pulmonary artery pressure of ≥ 25 mm Hg beyond the third month of life. Although the exact incidence of pulmonary hypertension is unknown, European registries place the number somewhere between 0.48[6] and 0.70[7,8] cases per million children per year. Acute pulmonary artery hypertension in congenital heart disease occurs more frequently in children than adults, with an incidence of 2.2 per million children per year. Database studies have suggested the prevalence of hospitalized children with pulmonary hypertension as a comorbidity.[9,10]

INO

INO is a potent pulmonary vasodilator when delivered by inhalation. Endogenous nitric oxide or endothelium-relaxing factor is generated in vivo from L-arginine in the presence of nitric oxide synthase, and nitric oxide activates soluble guanylate cyclase, increasing intracellular cyclic guanosine monophosphate and inhibiting the entry of calcium into the cell.[11] Activation of K^+ channels leads to hyperpolarization of the pulmonary vascular smooth muscle, which causes relaxation and dilation of the vessel. The last component is stimulation of cyclic guanosine monophosphate-dependent protein kinase, which activates myosin light chain phosphate, leading to dephosphorylation and further smooth muscle relaxation.[11] This endogenous nitric oxide regulates vascular tone by causing relation of vascular smooth muscle (Figure 2). Exogenous INO delivered in

Dr Walsh is affiliated with Allied Health Professions, Liberty University School of Health Sciences, Lynchburg, VA.

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Correspondence: Brian K Walsh PhD RRT RRT-NPS FAARC, Liberty University School of Health Sciences, 1971 University Blvd, Center for Natural Sciences, Lynchburg, Virginia, United States, 24515. E-mail: bkwalsh@liberty.edu.

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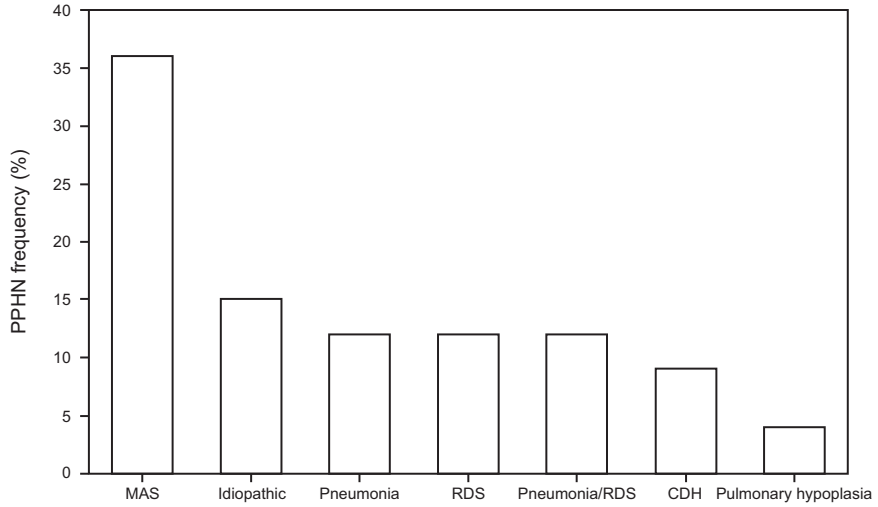

Fig. 1. Displays the frequency in percent of PPHN observed in neonates by respiratory disease. PPHN = persistent pulmonary hypertension of the newborn; MAS = meconium aspiration; RDS = respiratory distress syndrome; CDH = congenital diaphragmatic hernia.

parts per million (ppm) to ventilated areas of the lung provide a selective pulmonary vasodilation that acts by decreasing the pulmonary artery pressure and pulmonary-to-systemic arterial pressure ratio. Oxygenation improves as vessels are dilated, thereby redistributing blood flow from regions with poor ventilation and reducing intrapulmonary shunt. Nitric oxide combines with hemoglobin and is rapidly converted to methemoglobin and nitrate. As a result, there is little systemic effect. Nitric oxide also downregulates leukocyte response, decreases platelet aggregation, facilitates neurotransmission, reduces apoptosis, causes mild bronchodilation, and attenuates inflammatory response from cell injury after ischemia or tissue reperfusion.[11]

PPHN

PPHN occurs when pulmonary vascular resistance remains elevated following birth, resulting in a right-to-left shunting of blood through fetal circulatory channels. This leads to severe hypoxemia that can result in death. The prevalence of PPHN has been estimated at 1.9 per 1,000 live births.[5] Treatment of PPHN is largely supportive and includes INO, which improves oxygenation and reduces the need for extracorporeal membrane oxygenation (ECMO) in term and late-term infants with severe PPHN defined as an oxygen index $\geq$ 25 without a difference in mortality.[12-16] However, INO may not be effective in patients with milder PPHN, defined as an oxygen index of 15–25.[17]

Prematurity

Respiratory failure in premature infants is a result of primary ventilation-perfusion mismatch due to lack of surfactant and an underdeveloped pulmonary vascular system. Because pulmonary hypertension occurs in a small proportion of very low birthweight infants and is thought to be higher in prolonged premature rupture of the membranes,[18] it has been suggested that select application of INO in premature infants with oxygen index $>$ 25 with echocardiographic evidence of PPHN who are unresponsive to conventional respiratory care may benefit from INO therapy.[18,19] However, INO has not been found to be beneficial in larger retrospective case-control trials of premature infants and therefore is not routinely recommended for use in infants $<$ 34 weeks gestational age with hypoxemic respiratory failure.[20,21] Of note, INO exposure was associated

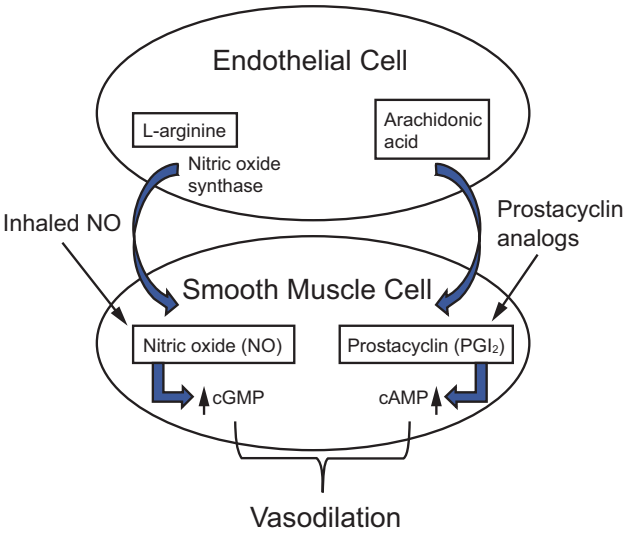

Fig. 2. Illustration of the vasodilatory pathways of NO (cyclic guanosine monophosphate [cGMP]) and PGI_2 (cyclic adenosine monophosphate [cAMP]).

with a higher mortality than those with respiratory distress syndrome alone.

Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia (BPD) is a chronic lung disease associated with prematurity and pulmonary hypertension. Advances in neonatal care have improved the survival of premature infants, but morbidity from BPD is significant and a diagnosis of pulmonary hypertension has been seen as high as 20% in preterm infants.[22] A number of randomized controlled trials have been conducted to evaluate the safety and efficacy of INO to prevent BPD and to reduce mortality in preterm infants at risk for respiratory distress syndrome.[23-30] Despite differences in study design, no benefit of INO over placebo has been observed, with the possible exception of African-American infants (see section on race below). However, available data do not show that INO prevents BPD.

Pulmonary hypertension is recognized as an important complication associated with BPD and develops in 20–40% of infants with BPD at some point in their initial neonatal ICU course.[31-33] Pulmonary hypertension is an important risk factor for morbidity and mortality.[31,33-35] Acute pulmonary hypertension crisis is a potentially fatal complication and can be triggered by multiple causes, including surgery or anesthesia, acute lung disease, fever, hypoxia, or hypovolemia. Transient acute pulmonary hypertension crises with hypoxemia can also be triggered by defecation or breath-holding. Avoiding these triggers is an important step in the treatment of infants with BPD and pulmonary hypertension. INO is often used for the treatment of acute and severe pulmonary hypertension crises.[36,37] After stabilization and the initiation of INO weaning, long-term pulmonary hypertension treatment such as sildenafil is commonly leveraged.

Race. A meta-analysis of 3 trials that enrolled preterm infants receiving respiratory support in which at least 15% of the INO and control groups (or a minimum of 10 subjects) were African-American indicated that African-American infants in the INO group had a lower risk of the composite outcome or BPD (risk ratio 0.77, 95% CI 0.65–0.91, $P = .003$; interaction $P = .02$) but not death alone.[38] However, conflicting results exist. In a retrospective cohort study of propensity score- and race-matched infants 22–29 weeks gestational age who had respiratory distress syndrome with PPHN reported that INO was not associated with improved outcomes in premature African-American neonates.[39] This led to the conclusion that off-label use of INO was not associated with improvement in outcomes of premature African-American neonates.

Combination of Surfactant and Nitric Oxide. In a multicenter trial of late surfactant of 511 extremely preterm infants (< 29 weeks gestational age) who were 7–14 d old and were mechanically ventilated, the group that received both INO and surfactant and controls treated only with nitric oxide had similar survival without BPD at 36 weeks post menstrual age (31% vs 32%) or at 40 weeks post menstrual age (59% vs 54%).[40] A subsequent report found no benefit for the combination therapy for the primary outcome of pulmonary morbidity.[41]

Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia is often a condition of underdevelopment of the ipsilateral and contralateral lungs, severe pulmonary hypertension, and left-ventricular hypoplasia or dysfunction that contribute to mortality and morbidity. The cross-sectional area of the pulmonary vasculature is reduced, resulting in a relatively fixed pulmonary hypertension. Although some degree of postnatal pulmonary vasodilation can occur, this adaptive mechanism is limited. This results in altered oxygenation and ventilation and can increase the right heart failure and other organ damage. INO has been studied several times and does not appear to have long-term benefits. Despite the evidence, INO administration is widespread in patients with congenital diaphragmatic hernia.[16,42-45] In a study evaluating high-frequency ventilation versus conventional mechanical ventilation, the investigators reported that 49% of subjects with congenital diaphragmatic hernia and pulmonary hypertension received INO.[46] Some centers have experienced an association with improved oxygenation and a decrease in ECMO use.[47] Yet, following the evidence, INO is difficult to recommend, although it may have a limited role in treating severe hypoxemia to enable safer transport or ECMO initiation.

Combination of INO and Milrinone. Despite advances in care and ventilation practices of patients with congenital diaphragmatic hernia, mortality continues to be high. In the presence of cardiac dysfunction, the phosphodiesterase-PDE3 inhibitor milrinone has been explored for its inotropic and vasodilator advantages. In a retrospective chart review of 2 regional perinatal centers, infants were classified into 3 groups: No INO, INO responders, and INO nonresponders. Oxygenation and hemodynamic effects of INO and milrinone were assessed with blood gases and echocardiography. Kumar et al[48] reported several important factors: 54% of infants with congenital diaphragmatic hernia received INO; 31% of these infants had improved oxygenation, although oxygenation response was not associated with a decrease in right-ventricular pressure or ECMO use; and 33% of the INO responders and 30% of the INO nonresponders received milrinone. Milrinone lowered right-

ventricular pressure and improved ejection fraction. INO response was associated with improved oxygenation due to milrinone and survival following ECMO (67% vs 20% among nonresponders). This led to the conclusion that INO in combination with milrinone may be associated with improved oxygenation and better survival after ECMO in neonates with congenital diaphragmatic hernia.

Pediatric ARDS

Pediatric ARDS represents a small portion of pediatric ICU admissions, but its management remains challenging. Pediatric ARDS is an acute lung injury caused by a set of direct lung injuries or indirect lung injuries. In a review of pediatric ARDS, lung injury etiologies were pneumonia (35%), aspiration (15%), sepsis (13%), near-drowning (9%), concomitant cardiac disease (7%), and other clinical conditions (21%).[49] INO is theoretically an ideal way to improve blood flow to the adequately ventilated regions of the lung, thereby shunting blood flow away from the more poorly ventilated regions, improving oxygenation, and potentially lowering toxic ventilator settings and F_{IO_2}. Three randomized controlled trials performed in pediatric ARDS indicate that, despite short-term oxygenation gains, which often feels like success, INO does not improve meaningful outcomes.[50-52] This conclusion was supported by a meta-analysis of children and adults with ARDS.[53] Therefore, INO is not recommended for routine use in pediatric ARDS.[54] However, INO may be considered in patients with pulmonary hypertension that is not caused by mechanical issues or severe right-ventricular dysfunction, or as a bridge to a higher level of support like ECMO.

Congenital and Acquired Cardiac Disease/Post-Cardiac Surgery

Pulmonary hypertension from vascular endothelial dysfunction has been a frequent complication following the repair of congenital heart defects, which is often exacerbated by cardiopulmonary bypass.[55] Several studies have suggested that INO could be lifesaving in treating refractory pulmonary hypertension.[56-58] Further exploration in 3 randomized controlled trials reported an improvement (ie, decrease) in mean pulmonary artery pressure,[59] systolic pulmonary artery pressure,[60] and shorter duration of mechanical ventilation.[61] While Day et al[60] also reported an improvement in gas exchange, INO did not improve pulmonary hemodynamics and gas exchange immediately following congenital heart defect repair, and there was no difference between groups at 1 h. Limitations of these studies have been discussed at length in a Cochrane review by Bizzarro et al,[62] who concluded that no difference was found with the use of INO in mortality, pulmonary hypertension crises, mean pulmonary artery pressure, heart rate, or P_{aO_2}/F_{IO_2}. The study of INO in congenital heart disease is complicated by the heart anomaly, medical management, and surgical approach. For these reasons, and considering the small and diverse congenital heart defect population spread around the world, high-level evidence is difficult to obtain. Current evidence is difficult to interpret regarding the effects of INO on significant outcomes such as mortality. Yet, because INO is considered safe, it should be considered as an adjunctive rescue therapy in the presence of pulmonary hypertension.

Dosing/Route/Weaning

Dosing of INO has been well studied from 1 to 80 ppm. Table 1 is a review of studies with specific dosing results. Several studies started with 20 ppm and quickly weaned to a lower dose,[63-65] with only 1 study experiencing early weaning failure if dosing was < 10 ppm.[66] Dosing > 20 ppm was associated with elevated methemoglobin levels and NO_2 and is therefore not recommended.[13,65-67] Low dosing of 1–2 ppm can often achieve pulmonary vasodilation without increasing the risk of NO_2 or methemoglobin while conserving resources.[64,65,68] There is less evidence regarding how to wean INO. Once oxygenation improves, INO can be rapidly weaned without difficulty to 5 ppm and discontinued within 5 d.[14] If weaning from INO fails within 5 d, the neonate is more likely to have an underlying cause of dysregulated vascular tone, such as alveolar capillary dysplasia,[71] severe lung hypoplasia, or progressive lung injury.

INO has been delivered via endotracheal tube, nasal CPAP,[72,73] noninvasive ventilation, and heated humidified high-flow nasal cannula (HFNC). DiBlasi et al[74] reported that set INO delivery with noninvasive methods may be higher than delivered nitric oxide (actual) dose to the lung depending on the device and leak. Noninvasive ventilation support appears to provide the closest set to delivery within clinically relevant dosing ranges. HFNC was the most variable method, leading the authors to conclude that adjustments may need to be considered, including manipulating setting, minimizing leaks, and possibly changing support.[74] Caution should be used when transitioning from an invasive delivery of INO to a noninvasive delivery because the actual dose to the patient's lungs may differ.

Clinicians have explored INO dosing outside of invasive delivery methods in the prevention of intubation for pulmonary hypertensive crisis or liberation from mechanical ventilation. In a study looking at postextubation INO delivery via HFNC following a Fontan procedure, the authors concluded that the use of INO via HFNC reduced the duration of postoperative intubation, pleural drainage, and hospitalization.[75]

INO Delivery Systems

Cylinder-Based Delivery. Cylinder-based INO delivery systems have been used since the early 1990s. These

Table 1. Inhaled Nitric Oxide Dosing Studies

Study	Initial Dose, ppm	Dosing Range	Dosing Conclusion
Kinsella et al[63]	20	6–20 ppm	20 ppm for 4 h followed by 6 ppm for 20 h of inhaled nitric oxide causes sustained clinical improvement and may reduce need for ECMO.
Miller et al[64]	2, 10, 20	2–20 ppm	Even 2 ppm caused selective pulmonary vasodilation.
Finer et al[65]	5–80	5–80 ppm	No difference in response between 5–80 ppm.
Beghetti et al[66]	15	1–80 ppm	Early attempts to wean below 10 ppm failed. Successful discontinuation of inhaled nitric oxide was at a mean of 3.9 ppm.
Demirakca et al[67]	20	1–80 ppm	Best dosage was 10 ppm for pediatric ARDS and 20 ppm for neonates.
Okamoto et al[68]	16	0.13–16 ppm	Gas exchange improvements at < 1 ppm
Davidson et al[13]	5, 20, or 80	5–80 ppm	Elevated methemoglobin levels $> 7\%$ and $NO_2 > 3$ ppm were observed in the 80-ppm group only.
Cornfield et al[69]	2 vs 20	2–20 ppm	2 ppm did not acutely improve oxygenation, but it did attenuate deterioration.
Clark et al[14]	20	5–20 ppm	Initial dose of 20 ppm for 24 h followed by 5 ppm for up to 96 h reduced need for ECMO.
Finer et al[70]	1–2 vs 10–20	1–20 ppm	No difference in low dose vs high dose.

ppm = parts per million
ECMO = extracorporeal membrane oxygenation

systems have evolved and are very reliable with many safety features. Recent advancements in more comprehensive data collection and transfer, improved mechanical ventilator compatibility with > 70 identified, longer battery life, and now magnetic resonance imaging capabilities continue to ensure proper and ideal INO delivery.[76] Delivery of INO by 800-ppm tanks continues to be the main delivery method within the neonatal ICU and the pediatric ICU. Recently, the Noxivent gas and $NOxBOX_i$ system has joined INOMAX and INOmax DS_{IR} Plus systems in providing INO.

Nitric Oxide Generators. Recent technology has been introduced in the arena of INO delivery. New companies have been able to enter the market by creating a generic option for INO, and others have developed strategies to create INO at the bedside. This new area of research and development has created a new category of INO delivery called nitric oxide generator systems (Figure 3). Companies leading the advancement of INO delivery include AIT Therapeutics, VERO Biotech, Third Pole Therapeutics, and Nu-Med. In this category, VERO Biotech employs the only FDA-approved system (ie, GENOSYL) that produces INO in a reactor cartridge using liquid N_2O_4 to generate nitric oxide without tanks.[77] The system uses an antioxidant reactor scrubber that minimizes NO_2. The AirNOvent (AIT Therapeutics)[78] and eNO (Third Pole Therapeutics)[79,80] are capable of generating INO from ambient air using an electrical discharge (plasma/iridium spark) to create NO_2, which is converted to nitric oxide using a scrubber that requires daily changing. This on-demand system can produce concentrations of 1–400 ppm without the use of tanks. The Nu-Med plus delivery system includes a cartridge technology about which there is little publicly available data.[81]

Inhaled Prostacyclin

Prostacyclin is synthesized primarily by vascular endothelial cells and is a ligand for the prostacyclin receptor, which is expressed in multiple organs including the pulmonary arteries. Prostacyclins are prostanoids derived from arachidonic acid by the vascular endothelium and are signaling molecules. Their functions are mediated through G-protein receptors on pulmonary endothelial cells, increasing the intracellular cyclic adenosine monophosphate activation of protein kinase A, leading to smooth muscle relaxation. For pulmonary hypertension, the primary effect of inhaled prostacyclin receptor activation by the prostacyclin or its analogs is to induce pulmonary vasodilation (Figure 2). Prostacyclins function as potent vasodilators, inhibit platelet aggregation, and have antiproliferative and anti-inflammatory effects. As with INO, when delivered to ventilated areas of the lung prostacyclin provides a selective pulmonary vasodilation that acts by decreasing the pulmonary artery pressure and pulmonary-to-systemic arterial pressure ratio. Oxygenation improves as vessels are dilated, thereby redistributing blood flow from regions with poor ventilation and reducing intrapulmonary shunt and afterload of the right ventricle.

PPHN

Inhaled iloprost in neonates alone or in combination with INO has resulted in improvement in PPHN in a number of reports.[82-85] In a study of 47 neonates with PPHN, aerosolized iloprost was reported to be more effective than sildenafil in time to and duration of intended clinical response, and the iloprost group had less need for inotropic support.[83] Iloprost was used in 15 preterm infants with respiratory

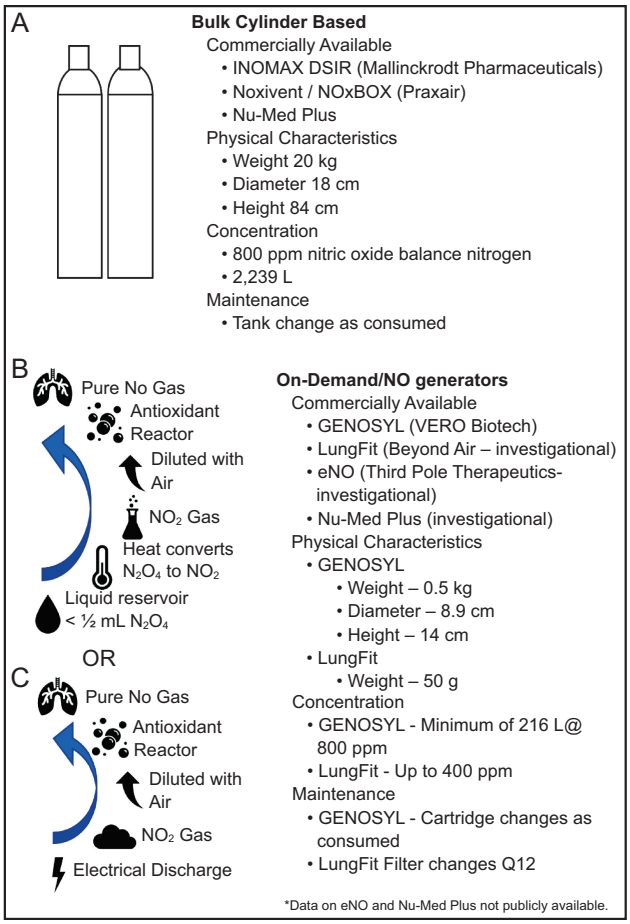

Fig. 3. A: Cylinder-based inhaled nitric oxide delivery devices commercial availability, physical characteristics, concentrations and maintenance, if known. B: Illustration of the chemical reaction used to generate inhale nitric oxide at the point of care, commercial availability, physical characteristics, concentrations, and maintenance, if known. C: Illustration of the electrical discharge that can produce inhale nitric oxide at the point of care, commercial availability, physical characteristics, concentrations, and maintenance, if known.

distress syndrome and pulmonary hypertension who were unresponsive to surfactant replacement and conventional mechanical ventilation.[84] The authors concluded that iloprost in severely ill premature neonates with pulmonary hypertension was beneficial, with high tolerability and a low incidence of systemic side effects.

Pediatric ARDS

Several small studies have evaluated the hemodynamic effects of continuously nebulized epoprostenol in children,[86] but only 1 study discussed its use for pediatric ARDS.[87] Dahlem et al[87] reported a 26% improvement in the oxygen index compared with the placebo cohort. The authors also concluded that only 1 subject needed to be treated (ie, number-needed-to-treat) to observe a 20% increase in oxygen index.[87]

Acute Pulmonary Hypertension

Inhaled epoprostenol was evaluated by Brown et al[88] for the management of acute pulmonary hypertension in 13 neonates and 7 pediatric (> 30 d old) subjects. The authors reported a significant improvement in oxygen index from 25.6 to 14.5 ($P = .02$); however, this significant improvement was not observed in pediatric subjects (29.6 vs 25.6, $P = .56$). This led the investigators to conclude that neonates may benefit more from inhaled prostacyclin than older children.[88]

Rimensberger et al[89] compared INO with iloprost for the treatment of secondary pulmonary hypertension in children with congenital heart disease. The authors reported that both INO and iloprost effectively lowered pulmonary vascular resistance. In a second and smaller study, Vorhies et al[90] validated Rimensberger's findings by transitioning postoperative pulmonary hypertension subjects from INO to inhaled iloprost. No differences were found in pulmonary artery pressure and systemic artery pressure.

Treprostinil is the newest of the prostacyclin analogs and was approved similarly to iloprost for pulmonary hypertension to help improve exercise capacity[91]; however, it has not been evaluated for use in critically ill neonatal or pediatric subjects with acute pulmonary hypertension or lung disease. Krishnan and colleagues[92] described the safety and efficacy of inhaled treprostinil in a retrospective analysis of 29 children with pulmonary hypertension, reporting a significant improvements in 6-min walking distance.

Pulmonary Hypertension Not Responsive to INO

Because the prostacyclin analog works on a separate pathway from INO (cyclic adenosine monophosphate vs cyclic guanosine monophosphate) to generate vasodilation, clinicians have been tempted to use prostacyclin in patients who are not responsive to INO. In a small case report, Kelly et al[93] reported on the use of epoprostenol in 4 neonates refractory to INO alone. All but 1 subject survived, and the infant that died was found to have alveolar capillary dysplasia. However, Rimensberger et al[89] did not find that a combination of both vasodilators improved pulmonary hypertension than either substance alone.

Pharmacodynamics and Dosing

Epoprostenol, iloprost, and treprostinil dosing is different. Ideal dosing in the pediatric population remains unclear, particularly in the neonatal and pediatric intensive care environment, where breathing patterns and weight vary drastically and the use of mechanical ventilation is prevalent. There are few studies about nebulizer comparisons of those used in the FDA approval process with commercially available nebulizers used in today's ICUs. Parker

Table 2. Prostacyclin Dosing Studies

Study	Prostacyclin	Half-Life	Dosing Range	Dosing Conclusion
Dahlem et al[87]	Epoprostenol sodium	6.5–10 min[95]	10–50 ng/kg/min	Significant improvement at 30 ng/kg/min
Loukanov et al[96]	Iloprost	21–25 min[97]	0.5 μg/kg	Favorable safety profile
Vorhies et al[90]			1.25–5.0 μg/kg	Similar results to inhaled nitric oxide
Krishnan et al[92]	Treprostinil	4.4–4.6 h[95]	18–54 μg, 4 times a day	Similar to adults with improved 6-min walk distance

et al[94] compared the vibrating mesh technology with the FDA-approved treprostinil inhalation system and reported that the vibrating mesh technology met or exceeded dose delivery. This led the authors to conclude the vibrating mesh technology is a suitable alternative to the ultrasonic treprostinil inhalation system. Further exploration of nebulizer placement and output is beyond the scope of this paper. Table 2 summarizes the studies that have been done related to dosing of prostacyclins.

Epoprostenol Sodium. Epoprostenol, the sodium salt of prostacyclin, was the first exogenous prostanoid used for the treatment of pulmonary hypertension.[98] Aerosolized epoprostenol is effective in improving oxygenation and lowering pulmonary vascular resistance. Because of epoprostenol's short half-life, it must be administered continuously, and the dosing is in ng/kg/min. Dosing ranges from 10 to 50 ng/kg/min with a bell-shaped response curve.[87]

Iloprost. Iloprost is a prostacyclin analog pharmacologically similar to epoprostenol. Iloprost has a lower viscosity, greater stability, lower pH, and longer half-life than epoprostenol.[86] This makes iloprost superior for inhalation. In the pediatric acute care setting, iloprost dosing ranges from 0.5 to 5 μg/kg,[90,96] with 1 study reporting a single dose of 25 ng/kg/min for 10 min.[89]

Treprostinil. Treprostinil is a prostacyclin analog similar to iloprost and is chemically stable with a much longer half-life,[95] which leads to a more favorable and less labor-intensive administration schedule.[99] However, the data on inhaled treprostinil are very limited.[100] In a retrospective analysis of 29 children with documented World Health Organization Group 1 pulmonary hypertension, inhaled treprostinil starting at 3 breaths 4 times a day and titrated as tolerated to a maximum of 9 breaths 4 times a day (or 18–54 μg/dose).

Experimental Nitric Oxide Generators

Nitric Oxide Generation

In addition to the nitric oxide generators in the previous section about new INO delivery devices, there are a few additional experimental nitric oxide generators showing promise. Qin et al[101] presented a portable nitric oxide generator that produces nitric oxide at the surface of a large mesh of working electrodes by electrochemical reduction of the nitrite ion in the presence of a soluble copper (II)-ligand electron transfer mediator complex. Nitric oxide generated with this system is transported by purging with a nitrogen and air combination. Gas phase nitric oxide concentrations range from 5 to 1,000 ppm.

Lautner et al[102] reported the use of narrow-band light-emitting diode (LED) light sources to achieve photolytic release of gas phase nitric oxide from polydimethylsiloxane, S-nitroso-N-acetylpenicillamine, and S-nitrosoglutathione films. The nitric oxide production can be controlled by the LED-triggered release. Gas phase nitric oxide concentrations range from 1 to 8,500 ppb. Much of this groundwork is laying the foundation for highly portable devices that may revolutionize treatment for the chronic pulmonary hypertension and cystic fibrosis populations.

Safety

INO

Potential toxicity of INO includes methemoglobinemia secondary to excess INO concentrations. INO can combine with hemoglobin to form nitrosythemoglobin, which oxidizes rapidly to form methemoglobin; in excessive quantities (usually $> 15\%$), methemoglobin can cause hypoxia. If caught early, weaning of INO can typically resolve methemoglobin problems. Therefore, it is recommended to obtain methemoglobin levels within 4–8 h of initiation and then routinely during administration of INO.[103]

Nitric oxide is unstable in air and will directly convert to NO_2, which is toxic to the lung at levels of > 5 ppm.[104] NO_2 is known to induce airway inflammation and reactivity, as well as alterations in surfactant metabolism.[104] All INO delivery systems monitor for NO_2. Every effort should be made to reduce this toxic gas.

Some studies in adults have shown a risk of acute kidney injury during INO therapy,[105] yet a meta-analysis by Hu et al[106] indicated a lower risk of acute kidney injury following cardiopulmonary bypass in those receiving INO therapy. The mechanism of INO-related kidney injury is unclear as other studies have shown little risk after INO therapy.[107] For those with renal insufficiency, caution should be exercised to limit nitric oxide exposure.

Table 3. Adverse Event Profile

Modulation of Nitric Oxide (Cyclic Guanosine Monophosphate) Pathway	Modulation of Cyclic Adenosine Monophosphate Pathway*
Inhaled nitric oxide	Prostaglandin analogs
Cough	Hypotension
Bronchoconstriction	Drug tolerance
Methemoglobinemia	Nausea/vomiting
Tolerance development	Headache
Nitrogen dioxide accumulation	Cough
Acute kidney injury	Jaw pain
Prolonged bleeding times	Flushing

*Adverse events related to central lines or associated pumps or systems were excluded.

Nitric oxide inhibits platelet adherence to endothelial cells as well as platelet-to-platelet aggregation.[108] A study of neonates treated with INO at 40 ppm for PPHN showed prolonged bleeding time but normal in vitro platelet function.[109] INO appears to be safe when administered in the established therapeutic dosing range of ≤ 20 ppm and with appropriate monitoring.[16,110] INO is approved by the FDA as a specific pulmonary vasodilator therapy for PPHN in term and near-term infants. Its use is based on extensive safety and efficacy data obtained from large placebo-controlled trials.

Because the half-life of INO is so short, when abruptly stopped, rebound pulmonary hypertension may develop, even if no improvement in oxygenation was observed at the onset of therapy.[111] This phenomenon can lead to life-threatening elevations in pulmonary vascular resistance and a decrease in oxygenation, but these effects can be avoided if the patient is weaned to 1 ppm before discontinuation.[112,113] Additionally, all available INO systems have an emergency back-up system to avoid abrupt discontinuation of therapy due to device failure. Please see the left side of Table 3 for observed adverse events associated with INO.

Inhaled Prostacyclin

It is important to note that no formulation of prostacyclin that is FDA approved for inhalation during mechanical ventilation or the pediatric population is currently available. There are 2 forms of prostacyclins that have been approved for aerosolization to improve exercise capacity for spontaneously breathing adults with pulmonary arterial hypertension of World Health Organization Functional Class III and IV disease severity. Therefore, only limited data are available on dosing and potential side effects. Data from adult drug trials list the side effects as hypotension, drug tolerance, nausea or vomiting, headache, cough, flushing, and jaw pain.[114] Please see Table 3 for observed adverse events associated with inhaled prostacyclins.

The prostanoids derive their selectivity for dilating the pulmonary vasculature by inactivation before reaching the systemic circulation. Should dosing exceed clearance capacity within the pulmonary vasculature, vasodilation of the systemic vasculature will occur and could lead to hypotension or exacerbate right-to-left shunt, particularly in patients with PPHN.

General-purpose nebulizers that are not specifically designed to deliver prostacylins increase the variability of dosing and expose patients to an additional risk when precise drug delivery is required. This could exacerbate hypotension by providing a dose larger than the clearance capacity or by failing to reach a therapeutic dose if the output is lower than intended. In the neonatal and pediatric critical care environment, the risk of providing an off-label drug through an off-label drug delivery device must be careful weighed against the benefit of such therapy.

Epoprostenol was never intended for inhalation application, and its only available preparation is for intravenous use. Epoprostenol's short half-life requires staffing and an emergency back-up device and power source to be immediately available to ensure there are no life-threatening drug-delivery interruptions. Epoprostenol's diluent has a pH of 10.2–10.8 and is hypotonic, which is potentially caustic to the airways and may result in injury. With the availability of inhaled preparations of long-acting prostacyclins like iloprost and treprostinil, epopropstenol should no longer be used.

Value

Off-Label Use

The rates of off-label INO use in preterm infants continue to rise despite evidence revealing no clear benefit in this population. This pattern of INO prescription is not benign and comes with economic consequences.[115] In children with acute lung injury, INO was not associated with improvement in mortality, but it was associated with increased hospital utilization and hospital costs.[2] The belief that pulmonary vasodilators are required or the allure of improved oxygenation has driven clinicians to utilize cheaper and less proven inhaled vasodilators such as iloprost or treprostinil.

Cost Savings

Because INO costs are often high, its use gets a lot of attention. Several institutions have explored ways to reduce this cost without negatively affecting patient outcomes. Elmekkawi et al[116] developed an INO stewardship program

designed to promote an evidence-based practice. The introduction of INO stewardship was associated with improved adherence to evidence-based guidelines and an overall reduction in total and per-patient INO use.[116] As with most protocols in respiratory care, they have been associated with decreases in direct costs. Todd Tzanetos et al[1] reported that the implementation of an INO protocol within the pediatric ICU reduced the cost of therapy without changing mortality compared to nonprotocolized care. Walsh and Rettig[117] questioned the protocolization of unproven therapy. Cost may be drastically reduced if you do not start the therapy from the beginning.

Competition within the INO market will hopefully provide additional opportunities to reduce cost. INO cost by consumption and not by the hour regardless of consumption may drive clinicians to titrate doses to the minimum therapeutic response dose. Finer et al[70] reported that 1–2 ppm was no different than 10–20 ppm. If cost becomes based on consumption of tanks, cartridges, or filters, this would save institutions money and potentially reduce adverse events, creating a win–win situation.

Summary

INO is the only FDA-approve pulmonary vasodilator for the neonatal and pediatric ICU for infants > 34 week gestational age with severe PPHN (ie, oxygen index > 25). INO dosing and safety profiles are well understood due to well-designed, high-quality studies in the neonatal population. Uses of INO outside of its FDA-approved use are controversial and should be only considered as a rescue modality in patients who are not responding to conventional therapy. Additional study is needed to determine the effectiveness of INO in off-label applications with an eye toward cost/benefit ratios. Advancements and competition within INO delivery device markets will bring some welcomed options to the neonatal and pediatric ICUs.

Inhaled prostacyclins appear to be an alternative that can provide pulmonary vasodilator effects equal to those of INO at a reduced cost. However, significant concerns about dosing and safety within the neonatal and pediatric populations should limit their use. Additional study is needed to determine whether the use of inhaled prostacyclins are safe and effective with currently available nebulizers, mechanical ventilation (invasive and noninvasive), and HFNC delivery devices for acute pulmonary hypertension in the neonatal and pediatric ICUs. Epoprostenol should not be utilized in the face of having FDA-approved iloprost and treprostinil preparations designed for inhalation, albeit in the adult population. Epoprostenol was never designed for inhalation, and the risks of the preparation outweigh the benefits, especially when alternatives exist.

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