Therapeutic Gases for Neonatal and Pediatric Respiratory Care

Timothy R Myers RRT-NPS

Though oxygen is the most frequently administered gas in respiratory care, the use of other specialty gases has become common practice in neonatal and pediatric intensive care and emergency departments across the United States. This report reviews the literature and evidence regarding 4 such specialty gases: heliox (helium-oxygen mixture), nitric oxide, hypoxic gas (ie, < 21% oxygen), and carbon dioxide. Because heliox is less dense than air or nitrogen, it offers less resistance and turbulence as an inhaled gas and therefore decreases the pressure and work of breathing necessary to ventilate the lung, which assists in the management of conditions that involve airway obstruction. Inhaled nitric oxide is a selective pulmonary vasodilator and during the last 2 decades research has focused on its potential value for treating disorders that involve pulmonary vasoconstriction. Hypoxic gas and carbon dioxide are used in the management of infants suffering hypoplastic left heart syndrome (a congenital heart defect), to equilibrate the pulmonary vascular resistance with the systemic vascular resistance, which is necessary to assure adequate oxygenation and tissue perfusion. Balancing the systemic and pulmonary vascular resistances requires increasing pulmonary vascular resistance and decreasing pulmonary blood flow; hypoxic gas does this by maintaining blood oxygen saturation at around 70%, whereas carbon dioxide does so by increasing P_{aCO_2} to the range of 45–50 mm Hg. *Key words: nitric oxide, hypoxic gas, heliox, hypoplastic left heart, respiratory failure, asthma, stridor, airway obstruction, croup, bronchiolitis, heliox, nitric oxide, neonatal, pediatric, carbon dioxide, hypoxic gas, respiratory, pulmonary.* [Respir Care 2003;48(4):399–422. © 2003 Daedalus Enterprises]

Introduction

Many of the original forerunners of today's respiratory care departments, arose during the 1940s from the need to provide supplemental oxygen to patients. At that time hospital oxygen supply systems consisted of high-pressure gas cylinders that required transport through the hospital and from patient to patient. The need for oxygen orderlies or oxygen technicians was born from this need to transport and provide supplemental oxygen in many hospitals. The growth of the respiratory care profession over the past 6 decades can be attributed in large part to advances in pulmonary therapeutics and medical technology. Though supplemental oxygen is still a mainstay of the profession of respiratory care, the need to provide additional supplemental gases to patients with cardiopulmonary disease has become a common adjunct to many etiologies. This review discusses the clinical evidence and delivery mechanisms for 4 specialty gases commonly used in acute and intensive care settings in many pediatric hospitals today: helium-oxygen mixture (heliox), inhaled nitric oxide, inhaled carbon dioxide, and hypoxic gas therapy.

Heliox Therapy

Introduction

Helium is an odorless, tasteless, nonexplosive, noncombustible, and physiologically inert gas. In 1935 Dr Alvan Barach first described the use of heliox as a possible treatment mechanism for cardiopulmonary disease.[1] Air flow through a fixed orifice or around an obstruction (ie, localized obstructive lesion) is always partially turbulent and inversely proportional to the square root of the gas density. Helium is one-seventh the density of atmospheric nitrogen, so it has a more laminar flow through a partially obstructed or fixed orifice, without a large difference in the viscosity of the gases. Table 1 compares the densities and viscosities of helium and the other primary atmospheric gases.

Since helium has no pharmacologic properties of its own, its therapeutic purpose is to lower the total density of the inhaled gas. For medical purposes helium is always mixed with oxygen and the mixture is commonly referred to as *heliox*. The higher the concentration of helium, the lower the fraction of inspired oxygen (F_{IO_2}) and the less dense the gas mixture. A basic understanding of respiratory and gas physics is necessary to understand the physical properties and behaviors that underlie the rationale for using heliox.

Table 1. Density and Viscosity of Helium and Other Atmospheric Gases

Gas	Density (g/L)	Viscosity (micropoise)
Helium	0.1785	188.7
Oxygen	1.4290	192.6
Nitrogen	1.2510	167.4
Air	1.2930	170.8

Respiratory and Gas Law Physics

The difference between the pressure at the airway opening and the alveolar pressure is the transrespiratory pressure, for both inspiratory and expiratory phases of normal respiration. That is: transrespiratory pressure equals the alveolar pressure minus the pressure at the airway opening. This equation is a crucial element in determining how much work must be done to ventilate the lung. A frequent factor associated with air flow obstruction is an increase in airway resistance, which is determined from the pressure gradient and is calculated by dividing the transrespiratory pressure by the flow of a gas traveling through that airway. Therefore, the effects of decreasing the gas density are not straightforward and are influenced largely by the characteristics of the airway flow.[2]

Three distinctly different patterns of pulmonary air flow affect airway resistance: laminar, turbulent, and transitional (ie, the transition from turbulent to laminar flow). The resulting flow patterns in the pulmonary system are the product of the physical conditions in the airway (airway diameter, anatomic shape, branching, smoothness of airway lining) and the composition of the inhaled gas. Typically gas flow in the lung periphery is laminar, primarily because of the large cross-sectional area through which the gas flows, whereas the flow in larger airways is mainly turbulent, because the flow is faster and through a relatively small cross-sectional area.

The Bernoulli principle asserts that as the pressure of a lateral wall drops, the velocity of gas within the tube increases. The Bernoulli principle as it relates to the airways implies that as gas velocity increases across a partial airway obstruction, the increased velocity causes airway tissues to be drawn further into the airway because of the

Timothy R Myers RRT-NPS is affiliated with the Department of Respiratory Care, Rainbow Babies and Children's Hospital, and with the Department of Pediatrics, Case Western Reserve University, Cleveland, Ohio.

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Correspondence: Timothy R Myers RRT-NPS, Department of Respiratory Care, Rainbow Babies and Children's Hospital, 11100 Euclid Avenue, mail stop 6020, Cleveland OH 44106. E-mail: timothy.myers@uhhs.com.

drop in lateral airway pressure. This phenomenon can worsen the partial airway obstruction (ie, bronchospasm, coughing, and airway edema), increasing the patient's work of breathing (WOB). Theoretically, when a less dense gas such as heliox is used, the gas requires less driving pressure and creates less velocity, which helps mobilize gas around an obstruction and ventilate the lung periphery. This decreases the WOB needed to produce the same or higher minute ventilation.

Another gas law that relates to the airways and heliox is the Graham law (principle of gas diffusion). The Graham law states that the diffusion rate of a gas is inversely proportional to the square root of its density. This principle means that a less dense gas has greater velocity or movement with less driving pressure.

Two other gas laws that correlate the airways' theoretical response to heliox are the Poiseuille law and the Reynolds number. The Poiseuille law describes the relationship between pressure, flow, and radius of the airway. This gas law principle as it relates to the airways can be simplified to 3 basic concepts: (1) A 50% reduction in air flow causes a 50% reduction in airway resistance and the flow requires much less pressure. (2) When air flow remains constant, each branch of the airway below the trachea requires a greater pressure (inversely to the 4th power of the airway radius) to move the same air flow through the smaller airways. (3) A 50% reduction in airway radius would increase resistance in the distal airways by 16 times.

The Reynolds number concerns the physical properties that influence the transition between laminar and turbulent flow:

Reynolds number = (flow rate × diameter × density)/viscosity

The variables that determine the conversion of laminar to turbulent flow in the airways are airway diameter, flow rate (inspiratory or expiratory), gas density, and gas viscosity. A Reynolds number $< 2{,}500$ promotes a laminar flow. A Reynolds number $> 2{,}500$ results in a turbulent flow, which requires a greater pressure gradient to ventilate the lung segment. Heliox, as a less dense and more viscous gas, will more easily pass around an airway obstruction than an oxygen-nitrogen mixture.

The physical properties of heliox, described by the gas laws, provide the rationale and theoretical basis for using heliox with respiratory diseases that are obstructive and promote turbulent air flow. The following section discusses the clinical indications for and ramifications of heliox in the neonatal and pediatric populations, as well as the mechanisms for delivering heliox.

Asthma

Asthma is one of the most common chronic diseases in pediatrics, today affecting an estimated 5 million children in the United States. Asthma is a chronic inflammatory disorder of the airways. In susceptible individuals this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli. Episodes are usually associated with air flow obstruction, which is often reversible, either spontaneously or with treatment. It is this air flow obstruction component of asthma that theoretically makes heliox an ideal treatment for pediatric asthma. Though the use of heliox in the management of acute exacerbations of pediatric asthma is relatively common, the evidence is largely anecdotal and its efficacy has not been demonstrated by large randomized, controlled trials.

Carter et al[3] investigated heliox's ability to improve pulmonary function, decrease dyspnea sensation, and decrease a clinical symptom score. In this prospective, double-blind, crossover study 11 patients were randomized to either 70:30 heliox or 30% oxygen for 15 min and then crossed over to the other treatment arm. All patients received 5 mg nebulized albuterol every 1–4 hours and intravenously administered methylprednisolone. Serial measurements of clinical and dyspnea score and spirometry values were obtained before and after treatment in each study arm. There was no significant difference with either scoring mechanism (clinical or dyspnea). There was no significant difference in forced expiratory volume in the first second (FEV_1) or forced vital capacity. Peak expiratory flow and forced expiratory flow in the middle half of the forced vital capacity ($FEF_{25–75}$) were significantly better in the patients who received heliox ($p = 0.04$ and $p = 0.006$, respectively). The authors concluded that short-term use of heliox did not benefit the management of pediatric status asthmaticus in that group of children.

Kudukis et al attempted to demonstrate the efficacy of heliox in reducing dyspnea and pulsus paradoxus in pediatric status asthmaticus.[4] In this double-blind, controlled trial 18 patients with status asthmaticus and pulsus paradoxus > 15 mm Hg were randomized to either 80:20 heliox or room air delivered via nonrebreathing face mask. All patients were treated with continuous β agonists and intravenous methylprednisolone. Patients receiving heliox had a statistically significant reduction in pulsus paradoxus, which increased with the discontinuation of the study gas ($p < 0.001$). The patients receiving heliox also demonstrated a significant increase in peak expiratory flow ($p < 0.05$) and a significant decrease in dyspnea index ($p < 0.0002$), which increased with gas cessation. Anecdotally, the authors thought that heliox obviated intubation and mechanical ventilation with 3 of the patients. Kudukis et al concluded that heliox significantly lowered pulsus paradoxus, increased peak flow, and lessened the dyspnea index in children with status asthmaticus.

Postextubation Stridor

Postextubation stridor is another situation in which airway obstruction causes turbulent air flow. The obstruction is caused by airway edema in the vocal cord region, secondary to the placement of an artificial airway. Frequently the removal of the artificial airway results in a temporary obstruction from soft tissue swelling that may or may not result in some degree of reversible air flow obstruction. Heliox provides more laminar air flow in this situation, which may alleviate clinical signs and symptoms.

Kemper et al assessed heliox for reducing postextubation stridor in children with burns and trauma.[5] This randomized, blinded trial included children ($<$ 15 years of age) who were electively extubated and had symptoms of postextubation stridor and an oxygen requirement of $<$ 35%. Study gas was administered for 15 min. A physician blinded to the treatment arm assessed study participants for respiratory distress. The study encompassed 13 children with 15 total extubations. Forty-seven percent (7 of 15) of the patients required subsequent treatment with racemic epinephrine or reintubation. A statistically significant decrease ($p < 0.005$) in stridor score (2.8 vs 3.7) was found among the patients receiving heliox. Anecdotally, in 8 of the 9 trials the physicians preferred heliox. Kemper et al concluded that heliox decreased stridor score among children with postextubation stridor and was a preferred treatment method.

In another study of postextubation stridor, Rodeberg et al assessed the effectiveness of heliox with postextubation burn patients.[6] In this small study, 8 pediatric burn patients who had postextubation stridor and retractions refractory to racemic epinephrine were treated with heliox. Patients were treated for 28 $\pm$ 5 hours with an initial helium concentration between 50% and 70%. In this study of convenience, 2 of the 8 patients required reintubation. In the other 6 patients the authors noted a decrease in respiratory distress score (6.8 $\pm$ 0.7 vs 2.0 $\pm$ 0.7). The authors concluded that heliox relieves stridor and prevents the need for reintubation in the majority of patients.

Airway Obstruction

There are a number of etiologies other than postextubation stridor that can result in upper airway obstruction. Viral tracheobronchitis and subglottic injury can cause upper airway obstruction that results in turbulent flow. Frequently the insertion of an artificial airway is the only mechanism to protect the airway. Intubation may lead to further inflammation, mucosal ischemia, subglottic swelling, and/or stenosis. Heliox promotes laminar air flow, which helps to alleviate clinical signs and symptoms and thus may obviate intubation.

In a study by Connolly and McGuirt,[7] 14 consecutive patients with severe airway distress and who met criteria for intubation were treated with heliox as their initial therapy. Four of the 14 (29%) patients (3 of whom had histories of subglottic stenosis) required intubation. The other 10 were successfully managed without intubation. The authors concluded that heliox is a relatively safe and effective alternative to intubation for children with severe subglottic edema or injury.

With a larger cohort of patients with upper airway obstruction, Grosz et al retrospectively evaluated the effects of heliox in 42 patients (over a 3 year period).[8] The retrospective analysis included children between the ages of 1 and 14 who were admitted and treated with heliox (44 occurrences) for upper airway obstruction. A positive heliox response was determined by a reduction in the WOB. Under that criteria, 32 of the 44 patients (73%) responded positively to the heliox treatment. There were no significant demographic differences between the groups except that all of the premature infants were responders and 6 of the 9 nonresponders were children with congenital syndromes. The authors concluded that heliox is effective and useful as an adjunct therapy for upper airway obstruction.

Croup

In a case series report, Duncan evaluated 7 patients suffering acute airway obstruction: 2 of the cases were caused by croup and the others by mass effect or postextubation edema.[9] In that series the mean croup score of 7.9 decreased to 3.9 after heliox administration (a statistically significant change). In another case series report of 14 patients (ages 3–21 mo) admitted to the hospital with the diagnosis of croup, the patients demonstrated reduced respiratory distress almost immediately after receiving heliox.[10]

In an emergency department pilot study by Terregino et al,[11] 15 subjects (mean age 24 mo) presenting with signs and/or symptoms of croup were enrolled into one of 2 groups: patients received either 30% oxygen (humidified) or 70:30 heliox (humidified). These authors found heliox to be safe, well tolerated, and as effective as humidified oxygen in reducing the croup score. The authors concluded that assessment of patients by a croup scoring system and blood gas analysis suggests that heliox is a useful alternative to tracheotomy or tracheal intubation.

In a prospective, randomized, double-blind trial Weber et al compared the effect of heliox and racemic epinephrine on croup scores in children with moderate to severe croup.[12] This study randomly assigned children who had moderate to severe croup scores ($\geq$ 5) to one of 2 treatment arms in the emergency department or pediatric intensive care unit (ICU). All 33 patients were initially treated with humidified oxygen and 0.6 mg/kg of intramuscular

dexamethasone prior to being randomized to either heliox or racemic epinephrine treatments. The final analysis included 29 patients, because 3 were excluded for protocol violations and 1 for lack of documentation. Heliox and racemic epinephrine were both associated with reduction in croup score over time. There were no significant differences in mean croup score, oxygen saturation, respiratory rate, or heart rate between the groups at baseline or at the end of the treatment period. The authors concluded that the effects of racemic epinephrine and heliox were similar between groups.

Bronchiolitis

Bronchiolitis, a common condition, is inflammation of the respiratory bronchioles, which produces airway obstruction from bronchial wall edema and mucus occluding the airways. The main viral pathogens responsible for bronchiolitis are respiratory syncytial virus (RSV) and parainfluenza virus. The most common time of year to see bronchiolitis coincides with RSV infections (and many other viral infections), between December and April.

In a recent prospective, interventional, comparative study Martinon-Torres et al assessed the therapeutic effects of heliox in infants with bronchiolitis.[13] The study assessed 38 infants, between 1 month and 2 years old, consecutively admitted to a pediatric ICU with moderate to severe acute RSV bronchiolitis. The first 19 patients were enrolled in the control arm, in which they received nebulized epinephrine. The next 19 patients received the same treatment as the control arm, plus heliox through a nonrebreather face mask. At baseline the 2 groups were similar in demographics and acuteness of disease. Clinical score, heart rate, respiratory rate, and oxygen saturation improved in both groups. At 1 hour and at the end of the observation period the clinical score, heart rate, and respiratory rate were significantly improved in the heliox group than the control group. The length of stay was significantly shorter for the heliox group than the control group. The authors concluded that heliox improved clinical respiratory status with infants suffering moderate-to-severe RSV bronchiolitis. This improvement resulted in a reduction of clinical score, tachypnea, and tachycardia. The beneficial response was noted within the first hour and continued through the duration of the study. In addition, heliox resulted in a significantly shorter length of stay in the pediatric ICU.

Hollman et al sought to determine the efficacy of heliox with children admitted to the pediatric ICU with acute RSV bronchiolitis.[14] The study included both a randomized, double-blind, controlled, crossover study and a nonrandomized, prospective study. Thirteen patients were randomized to treatment with either heliox or air-oxygen mixture, in random order, for 20 min. Five nonrandomized patients received heliox as initial therapy. Clinical asthma score, respiratory rate, heart rate, and oxygen saturation (measured via pulse oximetry [S_{pO_2}]) were recorded prior to randomization and after each 20-min treatment period (heliox or air-oxygen mixture). Nonrandomized patients were studied 20 min into heliox delivery. Clinical asthma score decreased in all patients (mean 1.23, $p < 0.01$), as well as in randomized patients (mean 0.46, $p < 0.05$) who received heliox. Randomized patients with clinical asthma scores < 6 ($n = 12$) showed a positive correlation ($r^2 = 0.72$) for change in clinical asthma score with heliox administration ($p = 0.009$). Respiratory rate and heart rate decreased with heliox, but the decreases were not statistically significant. Hollman et al concluded that heliox improves overall respiratory status of children with acute RSV lower respiratory tract infection.

In another study of infants with bronchiolitis, Gross et al assessed the response of 10 infants (ages 1–9 mo) who were mechanically ventilated with synchronized intermittent mandatory ventilation and received the following gas mixtures for 15-min intervals: 50:50 nitrogen-oxygen, 50:50 helium-oxygen, 60:40 helium-oxygen, 70:30 helium-oxygen, and returned to 50:50 nitrogen-oxygen.[15] There were no significant differences in the outcome variables with any of the gas mixtures. The authors concluded that in mechanically ventilated children with bronchiolitis the various heliox mixtures, compared with 50:50 nitrogen/oxygen, did not result in a significant or noticeable decrease in ventilation or oxygenation.

Delivery

The delivery of heliox can be problematic for spontaneously breathing patients and patients who require mechanical support. The first problematic issue is the patient's F_{IO_2} requirement, which limits the helium concentration that can be administered. A patient with an F_{IO_2} requirement > 0.40 is unlikely to benefit from the limited amount of helium that could be mixed into the inhaled gas.

For spontaneously breathing patients, heliox is best delivered through a closed system. A simple definition of a closed system is one in which the delivery mechanism is not prone to problematic leaks or air entrainment. In a study published in *CHEST*, Stillwell et al sought to determine the effectiveness of various heliox delivery systems.[16] The study used 5 adult, spontaneously breathing volunteers and measured the density dependence at 50% of vital capacity. The mean $\pm$ SD density dependence at 50% of vital capacity with a nonrebreathing mask (1.32 ± 0.89) and simple mask (1.21 ± 0.87) were statistically greater ($p < 0.05$) than heliox delivered via nasal cannula (1.00 ± 0.13). The authors also studied oxygen hoods as a delivery mechanism for heliox. The nitrogen concentration in the study hoods progressively increased from top to bottom of

Table 2. Actual Flows for Oxygen-Calibrated Flow Meter with Various Helium-Oxygen Mixtures

Helium to Oxygen Ratio	Actual Flow (% of set flow)
80:20	180
70:30	160
60:40	140

the hood, indicating that the helium was more concentrated in the top of the hood. Stillwell et al concluded that the nonrebreathing and simple masks were probably satisfactory delivery system, that oxygen hoods may be suboptimal, and that nasal cannulae are ineffective.

Typically, the gas is administered with a face mask and reservoir bag. A Y-piece attachment can be placed between the mask and the reservoir bag so as to add a nebulizer for concurrent β agonist administration. This delivery system requires a 12–15 L/min flow to maintain reservoir bag inflation, in a continuous delivery format, which requires 2–5 size H cylinders per day. When using an oxygen-calibrated flow meter for heliox therapy, it is important to remember that the less dense gas (helium) causes the actual flow to be greater than the indicated flow (Table 2).

Heliox delivery can also be problematic for patients who require mechanical support. The delivery of heliox via noninvasive ventilation to adults has been reported[17,18,] but with pediatric patients the reports are mainly anecdotal or single-case design. The delivery of heliox during mechanical ventilation has also been documented to be problematic.[19,20] Ventilators are designed to mix air and oxygen, so adding a gas of a different density, viscosity, or thermal conductivity can affect both the delivered and measured tidal volume in volume-controlled ventilation. The problem of delivered tidal volume can be partially addressed by using pressure-controlled ventilation, as pressure sensors are not affected by gas composition, whereas volume sensors are affected. Correction factors are necessary to accurately calculate measured exhale volumes.[20]

Summary of Heliox

Heliox has gained widespread support and use in many pediatric emergency departments and ICUs over the past decade. Clinical evidence on the effectiveness of heliox is largely anecdotal, in case presentations or small, uncontrolled studies. Heliox has been touted and promoted as an adjunct to care for infants and children suffering both upper and lower airway obstruction. Heliox's ability, as a less dense gas, to promote a more laminar flow in obstructed airways has been purported to assist in reducing WOB, respiratory distress, and postextubation stridor.

Though the evidence appears to support the utility of heliox in postextubation stridor, upper airway obstruction, and possibly unintubated patients with bronchiolitis, the evidence is relatively sparse. The evidence for other pediatric obstructive disorders (croup, asthma, and mechanically ventilated bronchiolitis) is largely anecdotal or insubstantial. The cost of heliox, compared to racemic epinephrine, should be considered when initiating frontline therapy for obstructive airway disorders. Further randomized clinical trials with pediatric patients are needed to determine the utility and benefits of heliox therapy.

Nitric Oxide

Introduction

Nitric oxide (NO) is a lipophilic, endogenous, free radical compound that is naturally produced by most cells in the human body. In 1987 NO was identified as a potent vasodilator (via vascular smooth muscle relaxation) that could explain the mechanism of action of endothelium-derived relaxing factor.[21] Because of rapid oxidation of nitrates and nitrites, NO's biological half-life in human tissues is a matter of seconds.[22] Nitric oxide's primary mechanism of action is facilitated by binding to the heme moiety to cytosolic guanylate cyclase, causing an upsurge in the production of intracellular cyclic guanosine 3′,5′-monophosphate.

Nitric oxide's ability to relax vascular smooth muscle (and thus cause vasodilation), coupled with its short biological half-life, make it an ideal transcellular messenger. This led to the hypothesis by Zapol et al (cited by Hurford[23]) that the use of inhaled NO (INO) should diffuse the pulmonary vasculature of ventilated lung regions and cause pulmonary vascular smooth muscle relaxation, which would decrease pulmonary hypertension. INO diffuses through the alveoli into the adjacent vascular smooth muscle, causing relaxation and vasodilation.

Vascular smooth muscle relaxation and decreased pulmonary hypertension are possible with intravenous vasodilators (nitroglycerin, nitroprusside, or prostacyclin), but those agents frequently cause overall systemic vasodilation and enhance blood flow distribution to perfused but nonventilated lung regions. This redistributed blood flow from nonselective pulmonary vasodilation to nonventilated lung areas increases right-to-left shunting and worsens P_{aO_2}. The distribution of INO to nonatelectatic, non-fluid-filled alveoli theoretically should result in optimal ventilation-perfusion matching and improved arterial oxygenation. The intravascular action of INO is limited because its active binding with hemoglobin rapidly deactivates it and confines the vasodilatory capacity of INO largely to the pulmonary vasculature.[24,25]

Though INO has a clinically important therapeutic role as a specialty gas, it can have toxic effects. NO's high binding affinity for hemoglobin can form methemoglobin. High concentrations of INO or inefficient methemoglobin reductase activity can cause substantial methemoglobinemia.[26] Another potentially toxic effect from INO is a result of the delivery method. Though NO is normally oxidized into nitrite and nitrate, further oxidation of NO results in the toxic formation of nitrogen dioxide.[27,28]

Since the initial studies of INO in the laboratory and with adult patients with primary pulmonary artery hypertension were performed, hundreds of other studies have been conducted to determine the potential clinical applications of INO.[29] The following section reviews the clinical indications for and ramifications of INO for the neonatal and pediatric population, and the mechanisms for delivering INO.

Use in the Neonatal Population

Hypoxic Respiratory Failure. Hypoxic respiratory failure can occur as a primary developmental defect or as a comorbidity from a secondary disorder (persistent pulmonary hypertension of the newborn [PPHN], meconium aspiration syndrome [MAS], sepsis, pneumonia, hyaline membrane disease, congenital diaphragmatic hernia [CDH], or pulmonary hypoplasia). The Neonatal Inhaled Nitric Oxide Study Group (NINOS)[30] and the Clinical Inhaled Nitric Oxide Research Group Initiative studies[31] provide the best examples of INO's beneficial effects on oxygenation and on reducing the need for extracorporeal membrane oxygen (ECMO) with infants suffering hypoxic respiratory failure.

The NINOS[30] was a multicenter study to determine if INO would reduce mortality or the initiation of ECMO among infants suffering hypoxic respiratory failure. Infants < 14 days old and ≥ 34 weeks gestational age and whose oxygenation index (OI) was ≥ 25 were randomized blindly to receive either 20 ppm INO or to a placebo control of 100% oxygen. The study enrolled 121 infants in the control group and 114 infants in the INO group. Sixty-four percent of the patients randomized to the control group required the initiation of ECMO, whereas 46% of the patients randomized to the INO group required ECMO ($p = 0.006$). There was no significant difference in the overall mortality between the treatment groups. The NO group demonstrated significantly greater improvement in P_{aO_2} ($p < 0.001$) and a significant decrease in OI ($p < 0.001$). The authors concluded that INO decreased the need for ECMO but had no apparent effect on mortality.

The Clinical Inhaled Nitric Oxide Research Group Initiative was a double-blind, randomized, placebo-controlled study enrolling full-term and near-term infants with persistent pulmonary hypertension or hypoxic respiratory failure.[31] Patients were randomized to either 20 ppm INO or placebo gas. Patients that demonstrated $P_{aO_2} > 60$ mm Hg were weaned to 5 ppm INO. The INO group had significantly less need for ECMO ($p < 0.001$). INO also significantly improved P_{aO_2} and the alveolar-arterial oxygen difference and decreased OI. There was no significant difference in mortality rate or length of hospital stay between the 2 study groups.

A number of studies and a meta-analysis have found that INO improved oxygenation (P_{aO_2}) and reduced the need for ECMO in term and near-term (> 34 wk gestational age) infants.[32–38] INO alleviates PPHN by dilating pulmonary arteries and thereby reducing pulmonary vascular resistance (PVR) in well ventilated regions of the lung, redistributing pulmonary blood flow away from regions of low ventilation-perfusion ratio toward regions of higher ventilation-perfusion ratio. The success of INO in reducing the need for ECMO is similar to the success that has been documented by several institutions with high-frequency oscillatory ventilation (HFOV). These therapies decrease length of stay and overall cost of care for those infants who respond, as well as assisting in the avoidance of ECMO.[39,40]

In a multi-city study by Kinsella et al, the authors attempted to determine the roles of INO and HFOV, alone or in combination, in the treatment of severe PPHN.[41] The study randomized 205 neonates to INO (20 ppm for 4 h and then 6 ppm) with conventional ventilation or HFOV without INO. The patients had a variety of disease etiologies (respiratory distress syndrome [RDS], MAS, PPHN, or pulmonary hypoplasia ["other"]) ($n = 43$) and CDH. A positive treatment response was defined as a sustained $P_{aO_2} \geq 60$ mm Hg. Those who did not positively respond were crossed over to the alternative treatment (treatment failure after crossover led to combination treatment with INO and HFOV). The 2 therapies were similarly effective in improving oxygenation ($p = 0.33$), but with some infants crossover to combination therapy improved oxygenation after neither INO nor HFOV had alone. Combination therapy was more effective with infants suffering RDS and MAS ($p < 0.05$), whereas INO (with or without HFOV) was more effective ($p < 0.05$) than HFOV alone in patients who did not have parenchymal lung disease (non-CDH pulmonary hypoplasia and idiopathic PPHN). The authors concluded that for severe PPHN HFOV *plus* INO is frequently more successful than either HFOV or INO alone.

The current recommended dosing model for INO was conceived from a study by Clark et al.[31] The authors sought to determine if low-dose INO would reduce the need for ECMO in infants suffering hypoxic respiratory failure. Infants < 4 days old and ≥ 34 weeks' gestational age and with OI ≥ 25 were randomized blindly to receive either INO or (placebo control) 100% oxygen. Infants random-

ized to INO received 20 ppm for 24 hours and then 5 ppm for no more than 96 hours. The study enrolled 122 infants in the control group and 126 infants in the INO group. Sixty-four percent of the control patients required initiation of ECMO, whereas 38% of the INO patients required ECMO ($p = 0.001$). There was no significant reduction in 30-day mortality in either group. The INO group had a significantly lower incidence of developing chronic lung disease (CLD) ($p = 0.02$).

Table 3 summarizes trials and other clinical experience with INO for hypoxic respiratory failure.

Congenital Diaphragmatic Hernia. CDH occurs in approximately 1 per 3,000–4,000 deliveries.[42] Newborns with CDH are born with an absent diaphragm, which allows intestinal contents to migrate into the thoracic cavity. CDH infants typically present with pulmonary hypoplasia, surfactant deficiency, and pulmonary hypertension. Pulmonary hypertension associated with CDH is difficult to manage, but INO has demonstrated a good success rate in the management of pulmonary hypertension, so INO may have a therapeutic role.

A case report by Leveque et al suggested that INO might play a therapeutic role in the preoperative stabilization and management of newborns with CDH.[43] The authors reported the effects of INO in the preoperative period of a 1.8-kg, 35-week gestational age, male infant with a severe left CDH. After 20 hours of mechanical ventilatory support and surfactant the patient began to deteriorate, with evidence of bi-directional shunting. The patient was placed on progressively increasing concentrations of INO, up to 60 ppm. INO was not effective initially, bringing only a small improvement in P_{aO_2}. However, the association of INO and a continuous infusion of alpostradil (PGE_1) caused a rapid and sustained improvement in hemodynamics and P_{aO_2}. The infant stabilized and this allowed a slight decrease in the amount of support, prior to having surgical repair in the 34th hour of life (while on 40 ppm INO). The infant was weaned from 40 to 15 ppm by the fourth day after surgery, but was markedly dependent on INO for oxygenation. The patient was eventually weaned off INO by day 15 after surgery. The authors believed the INO was useful in improving the patient's oxygenation, without systemic hypotension, allowing stabilization and CDH repair.

A number of clinical studies have failed to clearly demonstrate that INO is effective in the early course of treating CDH. However, in some case studies and studies of small sample size, INO was noted to improve oxygenation after weaning from ECMO support.[44–46] In the largest of these 3 studies, Karamanoukian et al[44] enrolled 8 infants with CDH and 1 with lung hypoplasia from ogliohydramnios to receive 80 ppm INO for 20 min prior to ECMO or after ECMO if pulmonary hypertension reoccurred. There was no clinical improvement in P_{aO_2}, S_{pO_2}, OI, pH, or P_{aCO_2} prior to ECMO. After decannulation from ECMO, INO significantly increased P_{aO_2}, S_{pO_2}, and OI ($p < 0.05$). The authors concluded that INO did not offer clinical improvement (P_{aO_2}, S_{pO_2}, OI, pH, or P_{aCO_2}), but may play a role in the management of recurrent pulmonary hypertension episodes in CDH infants after ECMO decannulation.

However, recently published randomized, controlled trials found that INO was not effective in infants with CDH.[41,47] In the randomized, controlled, double-blind study by the NINOS group, 53 CDH infants were enrolled to determine if INO would reduce mortality or the initiation of ECMO. Patients meeting entry criteria ($\geq$ 34 wk gestational age, $<$ 14 d old, and 2 OI measurements of $>$ 25 at least 15 min apart) were randomized to receive either INO (20 ppm) or 100% oxygen only (control group). If the patient did not respond completely ($>$ 20 mm Hg increase in P_{aO_2}), the INO could be increased to 80 ppm. The study failed to demonstrate a significant difference in either primary outcome (death at 120 d or ECMO initiation) between the 2 study groups. Also, the secondary outcomes (oxygenation variables, length of stay, and bronchopulmonary dysplasia) were not significantly different. The results suggested that INO was not effective in neonates with CDH.

In a randomized, controlled trial, Kinsella et al studied the effects of INO and HFOV together and alone in a variety of neonatal diseases (RDS, MAS, PPHN, or pulmonary hypoplasia ["other"]) and CDH ($n = 34$).[41] Patients were randomized to INO and conventional ventilation or HFOV without INO. A positive treatment response was a sustained $P_{aO_2} \geq 60$ mm Hg, and those who did not positively respond were crossed over to the alternative treatment (treatment failure after crossover led to combination treatment with INO and HFOV). Patients with the diagnosis of CDH responded significantly worse than those with other disease etiologies. Response rates for all treatment strategies (INO $<$ 10%, HFOV $<$ 10%, and INO plus HFOV $<$ 15%) were lower for CDH than for all other disease categories ($p < 0.05$). CLD (defined as requirement for supplemental oxygen after 28 d) was more frequent among CDH patients (41%, $p < 0.05$) than among all other groups (RDS = 21%, MAS = 17%, other = 14%). CDH patients (53%) also had a significantly lower overall survival (including those who received ECMO) than the other disease etiologies (RDS = 83%, MAS = 93%, other = 91%, $p < 0.001$).

In summary, INO has not proven to have benefit or efficacy in stabilizing or managing CDH. In a number of studies the use of INO for CDH had minimal effect on reducing initiation of ECMO[41,44,47] or on clinical variables (P_{aO_2}, S_{pO_2}, OI, pH, or P_{aCO_2}).[41,44,47] The use of INO after surgical repair may or may not be helpful in oxygenation after ECMO decannulation.[44–46] Table 4 summarizes trials and other clinical experience with INO for CDH.

Table 3. Summary of Trials and Other Clinical Experience with Inhaled Nitric Oxide for Hypoxic Respiratory Failure

First Author	Year	Design	Control	*n*	INO Concentration (ppm)	Outcome Variables	Outcome
Clark[31]	2000	Randomized double-blind,	Placebo	248	20 (initial), 5	ECMO rate, mortality rate, P_{aO_2}, OI, CLD, $P_{(A\text{-}a)O_2}$	Significant reduction in ECMO rate and CLD rate. Significant reduction in $P_{(A\text{-}a)O_2}$ at 1h. No difference in mortality rate.
Davidson[32]	1998	Randomized, placebo-controlled, double-blind, dose-response	Placebo	155	5, 20, or 80	OI, P_{aO_2}, SAP, MSI, ECMO rate, CLD	Significant increase in P_{aO_2} and sustained decrease in OI. Suggestion that ECMO may be reduced.
Hoffman[33]	1997	Retrospective, matched cohort	Normal therapy	50		P_{aO_2}, ECMO rate, IVH rate, CLD, hospital cost	Significant reduction in ECMO rate, CLD rate, and IVH rate. Significantly decreased hospital cost. Significant increase in P_{aO_2}.
Kinsella[41]	1997	Randomized	HFOV	43 of 205	20 (initial), 6	ECMO rate, mortality rate, P_{aO_2}, pH, P_{aCO_2}, MV days	Combination therapy significantly increased P_{aO_2} in infants with RDS and MAS. INO (with or without HFOV) increased P_{aO_2} significantly more than HFOV alone in patients without parenchymal lung disease.
Lonnqvist[35]	1999	Retrospective	None	10		OI, ECMO rate, cost	Significantly decreased OI. 50% less need for ECMO. Less expensive than ECMO on per-hour basis.
Mercier[36]	1998	Open-label, prospective	None	150	10–80	OI, ECMO rate	Effective dose range 5–20 ppm. Significantly improved OI based on disease (RDS, PPHN, or sepsis). Significantly less and not sustained OI in some diseases (CDH, MAS), 16% ECMO rate.
NINOS[30]	1997	Randomized, double-blind,	Placebo	235	20 or 80	ECMO rate, mortality rate, P_{aO_2}, OI, $P_{(A\text{-}a)O_2}$	Significant reduction in ECMO rate, P_{aO_2}, OI, and $P_{(A\text{-}a)O_2}$. No difference in mortality rate.
Roberts[37]	1997	Open-label, randomized	Placebo	58	80	ECMO rate, mortality rate, OI	Significantly less need for ECMO. No difference in mortality rate.
Wood[34]	1999	Open-label, randomized, dose-response	None	29	6 or 20 and 6	ECMO rate, mortality rate	No difference in ECMO or mortality rate for either dose

INO = inhaled nitric oxide
ECMO = extracorporeal membrane oxygenation
OI = oxygenation index
CLD = chronic lung disease
$P_{(A\text{-}a)O_2}$ = alveolar-arterial oxygen difference
SAP = systemic arterial pressure
MSI = major sequelae index
IVH = intraventricular hemorrhage
MV = mechanical ventilation
RDS = respiratory distress syndrome
MAS = meconium aspiration syndrome
HFOV = high-frequency oscillatory ventilation
PPHN = persistent pulmonary hypertension of the newborn
CDH = congenital diaphragmatic hernia

Chronic Lung Disease in Neonates. Chronic lung disease frequently occurs in term and preterm infants because of a variety of neonatal conditions and diseases (eg, MAS, RDS, pneumonia, congenital heart disease). CLD has numerous etiologies, including oxygen toxicity, barotrauma, lung immaturity, inflammation, and infection. Treatment of CLD requires a multifaceted approach and a variety of interventions and therapies. Newer strategies for infants diagnosed with CLD are centered on reducing the pulmonary inflammation that results from iatrogenic injury from mechanical ventilation and oxygen toxicity. It has been hypothesized that INO participates in the production of (pro-inflammatory)[48] and protection from (anti-inflammatory)[49] oxidative lung injuries, which are caused by various mechanisms.

Table 4. Summary of Trials and Other Clinical Experience with Inhaled Nitric Oxide for Congenital Diaphragmatic Hernia.

First Author	Year	Design	Control	*n*	Time Frame	INO Concentration (ppm)	Outcome Variables	Outcome
Frostell[46]	1993	Case study	None	1	NA	10–20	NA	Ventilatory support could be substantially reduced
Karamanoukian[44]	1994	Before and after	None	9	20 min before ECMO and 20 min after ECMO	80	P_{aO_2}, S_{pO_2}, OI, pH, or P_{aCO_2}	No clinical improvement in any outcome variable prior to ECMO. Significant increase in P_{aO_2}, S_{pO_2}, and OI after ECMO.
Kinsella[41]	1997	Randomized, controlled	Placebo	34	28 days	—	Sustained $P_{aO_2} \geq 60$ mm Hg, death, CLD, disease etiology	Compared to other diseases, CDH had significantly less INO response, significantly higher rate of CLD, significantly higher rate of mortality (including ECMO patients).
Leveque[43]	1994	Case study	None	1	15 days	5–60	NA	Improved oxygenation
NINOS[47]	1997	Randomized, double-blind	Placebo	53	120 days	20–80	Death, ECMO, oxygenation variables, LOS, CLD	No significant decrease in either mortality at 120 days or ECMO. No significant difference in oxygenation variables, LOS, or CLD.
Shah[45]	1994	Before and after	None	4	NA	5–80	Oxygenation	Temporary oxygenation improvement in 3 of 4 patients

INO = inhaled nitric oxide
NA = not applicable
ECMO = extracorporeal membrane oxygenation
S_{pO_2} = arterial oxygen saturation
OI = oxygenation index
CLD = chronic lung disease
CDH = congenital diaphragmatic hernia
LOS = length of stay

In a clinical trial to determine if low-dose INO would reduce the need for ECMO, Clark et al produced some interesting data related to the development of CLD.[31] The study randomized 248 neonates (INO = 126, control = 122) born at > 34 weeks' gestation, who were < 4 days old at randomization, and who had OI ≥ 25. All patients had clinical or echocardiographic evidence of pulmonary hypertension, without cardiac defect. Block randomization occurred across 5 disease etiologies (MAS, pneumonia, RDS, lung hypoplasia, or PPHN). INO was initiated at 20 ppm. After 4 hours the dose was decreased to 5 ppm if the infant was deemed stable ($P_{aO_2} > 60$ mm Hg and pH ≤ 7.55). If the infant did not meet those criteria, INO at 20 ppm was continued for 24 hours (or until, at 4-h assessment intervals, criteria were met). The INO could be returned to 20 ppm if P_{aO_2} fell below 60 mm Hg and F_{IO_2} was 100%. After 24 hours all infants on 20 ppm INO were decreased to 5 ppm. INO was discontinued when the F_{IO_2} was < 0.7, treatment had run 96 hours, or the neonate was 7 days old. The authors discovered that CLD developed at a significantly lower ($p = 0.02$) frequency in the INO group (7%) than in the placebo group (20%).

A study by Banks et al sought to determine the effect of INO on oxygenation in severe CLD.[50] In this open-label, noncontrolled study 16 preterm infants, 23–29 weeks' gestational age, 1–7 months old, were enrolled on meeting eligibility criteria (≥ 4 wk old, ventilator-dependent, mean airway pressure ≥ 10 cm H_2O, and $F_{IO_2} \geq 0.45$). Study patients received INO at 20 ppm for 72 h, and F_{IO_2} was titrated to maintain arterial saturation oxygen (S_{aO_2}) ≥ 92%. Infants with ≥ 15% reduction in F_{IO_2} after 72 hours received prolonged treatment with low-dose INO, weaning by 20% every 3 days, as tolerated. Eleven of the 16 children had a significant increase in P_{aO_2} (24 mm Hg, $p < 0.01$) after 1 hour but no significant change in P_{aCO_2}. Results after 72 hours of INO were similar: 11 of the 16 infants had ≥ 15% reduction in F_{IO_2}, and 7 of those 11 had ≥ 35% F_{IO_2} reduction ($p < 0.01$). Ten of the 11 infants who responded to INO after 72 hours had a sustained response and an overall decrease in mechanical support. Long-term outcomes (mean duration 27 d, range 8–90 d) of the INO responders included 4 extubations, 4 deaths, and 2 on long-term ventilation (all 5 nonresponders either died or were on long-term ventilation). The authors concluded that low-dose INO might improve oxygenation in some infants with severe CLD, allowing a decrease in F_{IO_2} and ventilator support.

Chronic lung disese often causes above-normal PVR, so the pulmonary vasodilator properties of INO may benefit

CLD management.[51–54] In the only study (of the 4 discussed here) that specifically targeted CLD and was not a single-patient case study, Longnqvist et al[51] identified significant oxygenation improvement (reduced OI) in 9 ventilator-dependent CLD infants (median postnatal age 4 wk, range 2–16 wk) ($p < 0.014$). P_{aO_2} returned to baseline with INO discontinuation in all patients except one. INO had no significant influence on P_{CO_2}. Optimal INO concentration and individual response differed among patients.

In summary, it has been postulated that INO participates in both production of and protection from oxidative lung injury, by various mechanisms. INO might benefit CLD as a pulmonary vasodilator and assist in reducing the PVR associated with CLD,[51–53] but this has not been verified by randomized, controlled trials. The development of CLD is often associated with oxygen toxicity and prolonged mechanical ventilatory support; INO may be beneficial in improving gas exchange in neonates with CLD, thereby decreasing their oxygen requirement and need for mechanical support.[31] Though the data supporting INO for CLD is promising, it is as yet inconclusive regarding efficacy because of the length of time for continuous treatment and the cost of INO. Additional clinical trials of low-dose INO for CLD are warranted. Table 5 summarizes trials and other clinical experience with INO for CLD.

Premature Newborns with Hypoxemic Respiratory Failure. In the past decade the development and use of antenatal corticosteroids and postnatal surfactant have reduced mortality among premature infants. Premature infants as young as 23 weeks' gestational age and weighing 500 g are routinely being resuscitated and saved from an early demise from respiratory failure. The difficulty lies in getting these premature infants off the artificial respiratory support before causing additional ventilator-induced or oxygen-induced damage. There is some evidence, which is increasing in volume in the literature, that INO has a role in managing hypoxemic respiratory failure with premature infants.

Two early reports indicated that INO immediately reduces oxygen requirement in hypoxemic respiratory failure in premature infants.[55,56] Peliowski et al[55] reported on 8 infants who failed to respond to conventional management and who had prolonged rupture of the membranes and ogliohydramnios and were treated with 20 ppm INO. All the infants showed significant improvement in OI ($p = 0.015$) and decreased mean airway pressure with INO.

More recently published randomized, controlled trials have produced conflicting evidence that INO may or may not improve oxygenation in premature infants suffering hypoxemic respiratory failure. Cheung et al, in an open-label study of 24 preterm infants, delivered 20 ppm INO to test for improved clinical outcomes in premature infants with hypoxemic respiratory failure.[57] The authors found significant improvement in OI and mechanical ventilator support (airway pressure and F_{IO_2}). Despite the significant decrease in oxygen requirement, there was no significant change in P_{aCO_2} or pH. The authors expressed concern with a high mortality rate (58%) and abnormal head ultrasound profile (74%) of the infants receiving INO.

Skimming et al also found significant increases in P_{aO_2}, S_{aO_2}, and transcutaneously measured arterial oxyhemoglobin saturation.[58] They randomly assigned 23 preterm RDS infants to receive either 5 or 20 ppm NO. INO treatment lasted 15 min and was preceded and followed by a 15-min control period. Neither of the NO concentrations made a significant difference. No residual effects of INO were detected 15 min after either dose was discontinued. The authors speculated that INO might be a useful adjunctive therapy for these preterm infants.

The largest trial to date with preterm infants was by Kinsella et al, who completed a multicenter, double-blind, randomized, controlled trial of 80 preterm infants (< 34 wk gestational age) with severe hypoxemic respiratory failure.[59] The infants were assigned to receive 5 ppm INO or placebo. Study results demonstrated improved oxygenation after 60 min ($p = 0.03$). There was no significant difference between the study groups with regard to mortality rate, incidence of pulmonary or intraventricular hemorrhage, or CLD. The authors concluded that in these preterm infants low-dose INO significantly improved oxygenation, did not affect mortality, did not significantly increase the risk of intraventricular hemorrhage, and possibly decreased the incidence of CLD.

From a different and negative perspective, in an open, randomized, controlled trial by Subhedar et al infants were treated with INO, dexamethasone, or neither to determine if either reduced the incidence of CLD or death in high-risk preterm infants.[60] The study block-randomized 42 infants (10 INO, 11 dexamethasone, 10 both, and 11 to placebo) ≤ 32 weeks' gestational age, mechanically ventilated, receiving surfactant, and at high risk. The INO group received 20 ppm INO and were weaned according to a "positive response" within the first 2 hours of treatment. A "positive response" was an OI reduction of 25% or an F_{IO_2} decrease of ≥ 0.10. If there was a positive response, the INO was weaned in increments of 5 ppm every 15 min, to a minimum of 5 ppm, which would be delivered for 72 h. If weaning off 5 ppm was unsuccessful, attempts were made every 24 h until successful. Intravenous dexamethasone was given at 12-hour intervals for 6 days (0.5 mg/kg/dose for first 6 doses and 0.25 mg/kg/dose for final 6 doses). The incidence of death and CLD were similar for infants treated with INO and controls. More infants treated with INO died (10 vs 7), but that difference was not significant. The incidence of death and CLD were similar for infants treated with dexamethasone and controls. The authors concluded that neither INO nor

Table 5. Summary of Trials and Other Clinical Experience with Inhaled Nitric Oxide for Chronic Lung Disease

First Author	Year	Design	Control	*n*	INO Concentration (ppm)	Outcome Variables	Outcome
Clark[31]	2000	Block randomization	Placebo	248	5–20	CLD	CLD was significantly less frequent in INO group (7%) than in placebo group (20%).
Banks[50]	1999	Open-label, non-controlled	None	16	5–20	P_{aO_2}, P_{aCO_2}	11 of 16 children had significant P_{aO_2} increase at 1 h, no significant change in P_{aCO_2} at 1 h. 11 of 16 infants had $\geq$ 15% F_{IO_2} reduction, and 7 of those 11 had $\geq$ 35% F_{IO_2} reduction ($p < 0.01$) at 72 h.
Longnqvist[51]	1995	Open-label, non-controlled	None	9	0–60	OI, P_{aO_2}, P_{aCO_2}	Significant improvement in OI
Thompson[52]	1995	Case study	None	1	—	Oxygenation, ECMO	Rapid oxygenation improvement, ECMO avoided
Abman[53]	1994	Open-label, non-controlled	None	6	20	Oxygenation death	Significant oxygenation improvement, no deaths
Hoehn[54]	1998	Case study	None	1	—	Oxygenation, ECMO	Oxygenation improvement, ECMO avoided

INO = inhaled nitric oxide
CLD = chronic lung disease
F_{IO_2} = fraction of inspired oxygen
OI = oxygenation index
ECMO = extracorporeal membrane oxygenation

dexamethasone reduced the incidence of death or CLD at 96 hours of age.

The Franco-Belgium Collaborative NO Trial Group studied 204 infants suffering respiratory failure.[61] The authors concluded there was no significant difference in OI reduction after 2 hours, between the INO group and controls, for the primary study group (preterm infants < 33 wk gestational age). However, the study did find a significant difference in OI, length of ICU stay, and mechanical ventilation days for near-term infants (> 33 wk gestational age). The authors concluded that low-dose INO for neonatal respiratory failure improves oxygenation and reduces length of stay and duration of mechanical ventilation. However, INO was not significantly beneficial to preterm infants.

In summary, several studies of premature newborns have demonstrated immediate improvement in oxygenation status with INO.[55,56] Larger randomized trials have equally demonstrated this improvement in oxygenation status but not in the survival rates of premature infants with hypoxemic respiratory failure.[58–61] The potential for intraventricular hemorrhage and the development of CLD is an extreme risk in this premature population, and the incidence of these was not increased in the larger, randomized, controlled trials, as had been previously found in observational reports.[57] Table 6 summarizes clinical trials of INO for premature newborns.

Use in the Pediatric Population

Pediatric Acute Respiratory Distress Syndrome. ARDS results from a series of complex cellular and biochemical events caused by a severe pulmonary or nonpulmonary injury. Ashbaugh et al first described this clinical syndrome in 1967 and characterized it by its clinical symptomology (marked hypoxemia, severe dyspnea, diffuse bilateral infiltrates, and a decrease in respiratory compliance).[62] ARDS can be caused by various diseases and traumas. Table 7 lists some of the risk factors.

Despite advances in technology (eg, mechanical ventilation, pulmonary mechanics monitoring, and radiographic imaging), the mortality rate associated with pediatric ARDS has not changed appreciably over the last several decades. ARDS is the most severe form of acute lung injury that affects the pediatric population, with mortality rates of 40–60%.[63] Intubation and mechanical ventilation are the main components of supportive therapy for ARDS. Though mechanical ventilation is a supportive therapy, it increases the risk of volutrauma and chronic lung damage. With such a high mortality rate and therapy that is largely sup-

Table 6. Summary of Clinical Trials of Inhaled Nitric Oxide for Premature Newborns

First Author	Year	Design	Control	*n*	INO Concentration (ppm)	Outcome Variables	Outcome
Cheung[57]	1998	Open-label, non-controlled	None	24	20	Mortality, OI, P_{aO_2}, P_{aCO_2}, pH, P_{aw}, F_{IO_2}	Significant improvement in oxygenation, OI, and P_{aO_2} at 1h. Significant decrease in P_{aw} and F_{IO_2} at 4 and 24 h. No significant change in P_{aCO_2} or pH. High mortality rate (58%) and abnormal head ultrasound (74%).
Franco-Belgium Collaborative NO Trial Group[61]	1999	Randomized, controlled	Placebo	204	10	OI, LOS, MV duration	Significant decrease in OI at 2 h, NICU LOS, and MV days for near-term neonates. No significant decrease in OI at 2 h for preterm neonates.
Kinsella[59]	1999	Double-blind, randomized, controlled	Placebo	80	5	Mortality, IVH rate and severity, MV duration, CLD	Improved oxygenation, no significant difference in mortality rates, CLD, pulmonary hemorrhage, or IVH.
Peliowski[55]	1995	Open-label, non-controlled	None	8	20	OI, P_{aO_2}, P_{aw}	Increased P_{aO_2}, decreased P_{aw}, improved OI. 50% of infants suffered IVH
Skimming[58]	1997	Randomly assigned	INO dose	23	5 or 20	P_{aO_2}, S_{aO_2}, P_{tcO_2}, dose-response	No difference in INO response at 5 or 20 ppm. Significant increase in oxygenation. Significant decrease in respiratory rate.
Subhedar[60]	1997	Block-randomization	Dexamethasone, INO + dexamethasone, or placebo	42	20	Death, CLD, CLD or death	Rapid improvement in oxygenation. No effect on incidence of CLD or death.

INO = inhaled nitric oxide
OI = oxygenation index
P_{aw} = airway pressure
F_{IO_2} = fraction of inspired oxygen
LOS = length of stay
MV = mechanical ventilation
NICU = neonatal intensive care unit
IVH = intraventricular hemorrhage
CLD = chronic lung disease
S_{aO_2} = arterial oxygen saturation
P_{tcO_2} = transcutaneously measured partial pressure of oxygen

Table 7. Risk Factors for Pediatric Acute Respiratory Distress Syndrome

Sepsis
Gastric aspiration
Pulmonary contusion
Burns
Toxic gas or smoke inhalation
Multiple urgent transfusions
Major multiple fractures
Near-drowning
Infectious pneumonias
Shock

portive in nature, there is a need to explore new ARDS therapies, including INO.

In the only randomized, controlled, double-blind study to date, Day et al sought to determine if INO could improve oxygenation and PVR in children with ARDS.[64] Twenty-four patients meeting ARDS criteria (positive end-expiratory pressure $>$ 6 cm H_2O and F_{IO_2} $>$ 50% for $>$ 12 h) were randomized to either 10 ppm INO (treatment group $n = 12$) or to conventional therapy alone (control group $n = 12$). After 24 hours the control patients were also placed on 10 ppm INO. (The 10 ppm value was selected based on a previous study by Day et al who demonstrated similar increases in systemic oxygenation and decreases in PVR between 11 and 60 ppm.[65]) Blood gas values for oxygenation and hemodynamic values were assessed at baseline, 1 hour after randomization, then at 24-hour intervals for the next 2 days.[64] Seven of the 12 INO patients showed $>$ 20% improvement in OI, whereas only 1 of the 12 control patients showed a $>$ 20% improvement ($p = 0.015$). However, the effect was not sustained after 24 hours of INO, compared to the control group (5 vs 4, respectively). Five of the 10 control patients who crossed over (after 24 h) to receive INO experienced a $>$ 20% improvement in OI at both the 1-hour (ie, 25 h after study randomization) and 24-hour (ie, 48 h after study randomization) measurements. Among the patients ran-

domized to INO, the ratio of PVR to systemic vascular resistance (PVR/SVR) was significantly improved at both 1 hour (0.47 ± 0.10 vs 0.31 ± 0.08, $n = 7$) and 24 hours (0.35 ± 0.07 vs 0.31 ± 0.08, $n = 6$). This study suggests that INO offers rapid, short-term improvement of OI and PVR in pediatric ARDS, but it does not provide sustained improvement. The authors concluded that INO may have a limited role in pediatric ARDS.

In 2 small, prospective, dose-response studies, Demirakca et al examined INO's effects on oxygenation and hemodynamics in pediatric ARDS.[66] Eight patients meeting ARDS criteria (acute onset, $P_{aO_2}/F_{IO_2} < 200$ mm Hg, bilateral infiltrates, absence of left atrial hypertension, and CLD) all received 20 ppm INO for 1 hour and then had INO dose alterations (range, 1–80 ppm). Seven of the 8 patients demonstrated a significant increase in P_{aO_2} ($p = 0.0004$), P_{aCO_2} ($p = 0.0021$), and mean arterial pH ($p = 0.0018$) after the initial hour. The authors noted that within 24 hours of INO treatment OI decreased by 56% ($p = 0.0004$), the alveolar-arterial oxygen difference decreased by 31% ($p = 0.0004$), and the systemic arterial pressure increased by 15% ($p = 0.0029$). Demairakca et al determined the minimum effective dose to be 10 ppm and documented a continual increase in oxygenation with INO administration.

Nakagawa et al also performed a prospective, dose-response study.[67] Fourteen patients (15 trials) received INO, starting at 10 ppm and increasing to 20, 40, 60, and 80 ppm, at 10-min intervals. Mean OI significantly decreased with 80 ppm ($p = 0.01$). Mean pulmonary artery pressure (PAP) also significantly decreased with 80 ppm ($p = 0.04$). Mean PVR decreased with 80 ppm ($p = 0.06$). Six trials (43%) showed an increase of ≥ 20% in the hypoxemia score. Maximum improvement in hypoxemia score and reductions in OI, PVR, and mean PAP occurred at 20–40 ppm. The authors concluded that 20–40 ppm INO is an effective strategy for pediatric ARDS.

Abman et al conducted an open, nonrandomized trial of 17 patients (10 with ARDS) who received 20 ppm INO and stable ventilator settings for 30 min.[53] Gas exchange and hemodynamic measurements were compared before and after INO delivery. Pulmonary artery pressure, pulmonary capillary wedge pressure, and cardiac index were measured in all ARDS patients. INO rapidly and significantly improved oxygenation in 15 of 17 patients: mean P_{aO_2} increased from baseline after 30 min ($p < 0.01$). INO significantly lowered mean PAP ($p < 0.01$) and intrapulmonary shunt ($p < 0.01$) without changing systemic arterial pressure or pulmonary capillary wedge pressure. Cardiac index increased by 14% ($p < 0.01$). The authors concluded that INO quickly improves oxygenation and lowers PVR without causing adverse hemodynamic effects in severe hypoxemic respiratory failure in pediatric patients.

A study by Sheridan et al assessed the effect of INO on intrapulmonary right-to-left shunting (P_{aO_2}/F_{IO_2} ratio) in children with severe ARDS precipitated by burns.[68] Eleven children were enrolled; their ages ranged from 11 months to 14 years and they had an average burn size of 64% ± 22% of body surface area. Nine of the children had inhalation injuries, 1 aspirated hot grease, and 1 aspirated hot water (one child was enrolled twice). Initial INO was set at 5 ppm (10 cases) or 10 ppm (2 cases), beginning on average 6.3 ± 5.5 (range 1–21) days after injury and continuing on average for 7.8 ± 7.2 (range 0.33–25) days. On enrollment the patients' oxygenation status reflected an average P_{aO_2}/F_{IO_2} of 95 ± 50 (range 34–187) mm Hg and a P_{aO_2} of 74.3 ± 25.6 mm Hg on an average peak inspiratory pressure of 42.9 ± 7.1 and a positive end-expiratory pressure of 9.4 ± 2.7 cm H_2O. P_{aO_2}/F_{IO_2} improved an average of 162 ± 214% (range, 0–682%). In those patients who responded to INO, the oxygenation improvement (P_{aO_2} and S_{pO_2}) was immediate. Eight of the 11 children survived. The 3 nonsurvivors were older (11.6 ± 2.3 vs 5.9 ± 4.6 yr, $p = 0.026$), trended toward a larger burn surface area (82% ± 19% vs 57% ± 19%, $p = 0.12$), trended toward a quicker initiation of INO (3.0 ± 1.7 vs 7.3 ± 6.1 d, $p = 0.08$), had similar admission P_{aO_2}/F_{IO_2} (100 ± 75 vs 93 ± 44, $p = 0.082$), but exhibited significantly less initial response in percentage of P_{aO_2}/F_{IO_2} improvement (7.3 ± 5.4% vs 213 ± 226%, $p = 0.026$). Sheridan et al concluded that INO played a useful role in the management of the patients participating in the study.

A study by Okamoto et al investigated the effects of INO on pediatric ARDS to determine a predictive response, the optimal concentration of INO, the effects of < 1 ppm INO, and the effects of INO on P_{aCO_2}.[69] This small study of 7 children examined the initial response to 16 ppm INO and the dose-response effects of 0.13–16 ppm INO. All 7 children responded with improved oxygenation status on 16 ppm INO. INO significantly increased P_{aO_2}/F_{IO_2} in the study patients. A correlation with P_{aO_2}/F_{IO_2} from baseline was observed ($r = 0.93$, $p < 0.01$). Dose-response tests demonstrated the optimal dose to be < 4 ppm in that study cohort. INO concentrations of < 1 ppm improved P_{aO_2}/F_{IO_2}. A slight decrease in P_{aCO_2} was also noticed with the use of INO.

Goldman et al performed a retrospective review study to determine if INO provided an early response, in a measure of reversibility of lung injury and patient outcome in pediatric ARDS.[70] This study of 30 infants and children (ages 0.08–13 years) with severe acute hypoxemic respiratory failure (mean alveolar-arterial oxygen difference 568 ± 9.3 mm Hg, P_{aO_2}/F_{IO_2} 56 ± 2.3 mm Hg, OI = 41 ± 3.8, and acute lung injury score of 2.8 ± 0.1) used 20 ppm INO. Response was determined after 60 min based on the percentage change in OI. Goldman et al discovered a significant association between early-response INO and pa-

tient outcome (Kendall's Tau Beta $r = 0.43$, $p < 0.02$). All of the patients who had a < 15% improvement in OI died. Survival was 36% among patients who had an OI improvement of 15–30%. Survival was 61% among patients who had an OI improvement of > 30%. Of the 12 survivors, 9 continued on INO and 3 progressed to ECMO. The authors concluded that a greater early response to INO appears to be associated with better outcome.

In summary, a number of studies of INO for pediatric ARDS have been recently published. In the only randomized, controlled study of INO for pediatric ARDS published to date, investigators observed a rapid improvement in oxygenation and a decrease in PVR.[64] Data from small-sample-size trials reveal that INO rapidly improves arterial oxygenation and hemodynamic stability for the majority of pediatric ARDS patients[53,65–70] but that the arterial oxygenation improvement is not sustained after 48–72 hours.[64] Table 8 summarizes trials and other clinical experience with INO for pediatric ARDS.

Pediatric Cardiac Surgery. The incidence of congenital cardiac defects is 1 per 100 deliveries.[71] Frequently, children who undergo cardiac surgery for congenital heart defects are at significant risk for elevated PVR, right ventricular failure, and/or pulmonary hypertensive crisis (PHTC). Postoperative management of cardiac surgery patients frequently consists of mechanical ventilation, high F_{IO_2}, inotropic and systemic vasodilator support, and lung recruitment strategies. The following section reviews the beneficial aspects and therapeutic potential of INO in the routine management of postoperative pulmonary artery hypertension.

In a prospective, open-label study by Miller et al, low-dose INO (2, 10, 20 ppm) together with high F_{IO_2} was evaluated in 10 infants (13 episodes) who were at high risk (high PAP [> 50% of systemic arterial pressure] and/or high PVR/SVR by echocardiography or cardiac catheterization) for postoperative PHTC after surgical repair of left-to-right shunt lesion.[72] In this study INO at 2–20 ppm acted as a selective pulmonary vasodilator for both PAP ($p = 0.02$) and PVR ($p = 0.03$), with a negligible decrease in SVR, and the initial PVR/SVR correlated well with the maximum pulmonary vasodilatory response ($r = -0.82$, $p < 0.001$). Patients who had initial PVR/SVR > 0.50 had significant decreases in both PAP ($p = 0.02$) and PVR/SVR ($p = 0.03$).

Journois et al studied 17 patients to determine if hemodynamic changes occur with low-dose INO for postoperative PHTC.[73] The measured hemodynamic values included heart rate, PAP, systemic arterial pressure, central venous pressure, left atrial pressure, urine output, and arterial and venous blood gases. Hemodynamic values were measured at baseline and 20 min after the initiation of 20 ppm INO. INO was continued until there was an absence of pulmonary artery hypertension for 6 hours. INO was increased to 80 ppm if there was continuation of low arterial or venous oxygen saturation or a high mean PVR/SVR. Hemodynamic values were recorded hourly. All patients experienced a decrease in pulmonary pressures, without significant changes in systemic pressures (mean PAP = –34 ± 21%). All patients experienced an increase in oxygen saturations (arterial saturation increased 9.7 ± 12%, venous saturation increased 37 ± 28%). The authors concluded that INO acts as a selective pulmonary vasodilator in children with congenital heart disease, and increased saturation values signified a selective lowering of PVR.

A study by Curran et al investigated the hemodynamic effects of INO in children with congenital heart disease and refractory hypertension.[74] Five patients with atrioventricular canal defect and pulmonary hypertension received INO after surgical repair and removal from cardiopulmonary bypass. Patients were placed on 20, 40, and 80 ppm INO for 5-min intervals and hemodynamics were continuously measured. In a second group ($n = 15$) of ICU patients with refractory pulmonary hypertension from congenital heart disease, INO was used after failure of conventional therapy. In the 5 intraoperative patients PAP decreased from 20.0 ± 2.2 mm Hg to 18.0 ± 2.8 mm Hg (difference nonsignificant) and there was no significant change in mean PVR or cardiac output. Among the 15 patients with refractory hypertension, 11 had a favorable response to INO. Eight patients with pulmonary artery catheters had a significant decrease in mean PAP (from 30.9 ± 5.8 to 23.1 ± 5.4 mm Hg, $p < 0.01$). The authors concluded that inhaled INO had minimal beneficial effect on PAP or cardiac output in infants who had undergone atrioventricular canal repair. In this study INO was effective in reducing PAP in selected postoperative patients with congenital heart disease and pulmonary hypertension.

Russell et al conducted a randomized, controlled, double-blind study of INO's effect on postoperative pulmonary hypertension in pediatric congenital heart defect patients.[75] The study included 39 infants and children (40 cases) and preoperative pulmonary hypertension (mean PAP > 50% of mean systemic arterial pressure) with congenital cardiac defects (4 patients were eventually eliminated from the data set). Immediately after cardiopulmonary bypass was ceased, patients were randomized to placebo (nitrogen) or INO (80 ppm) and F_{IO_2} of 0.90. Gas was delivered for 20 min, with hemodynamic monitoring at baseline (before administration of the study gas), 10 min, 20 min, and at 1 min after cessation of study gas. Thirty-six percent (13/36) of cases emerged from cardiopulmonary bypass with pulmonary hypertension. Of those 13 patients, 5 received INO and 8 received placebo. At 20 min the patients who received INO showed PAP decrease

Table 8. Summary of Trials and Other Clinical Experience with Inhaled Nitric Oxide for Pediatric Acute Respiratory Distress Syndrome

First Author	Year	Design	Control	*n*	INO Concentration (ppm)	Outcome Variables	Overall Mortality (%)	Outcome
Abman[53]	1994	Open, non-randomized	None	10 ARDS, 7 non-ARDS	10	pH, P_{aCO_2}, P_{aO_2}, OI, P_{aO_2}/F_{IO_2}, $P_{(A\text{-}a)O_2}$, $\dot{Q}_S/\dot{Q}_T$, SAP, PAP, CO, PVR	50	Significant decrease in PAP. Significant increase in CO. Significant, rapid improvement in P_{aO_2} and P_{aO_2}/F_{IO_2}. Decrease in mechanical ventilatory support. Non-ARDS patients had better outcomes.
Day[64]	1997	Double-blind randomized, controlled	Placebo	24	10	PVR/SVR, OI	45	Significant OI improvement with INO. 50% of controls crossed over and had significant OI improvement with INO. PVR/SVR significantly improved at 1 h and 24h with INO, but improvement was not sustained.
Demirakca[66]	1996	Prospective, dose-response	None	8	20	INO dose, OI, $P_{(A\text{-}a)O_2}$, SAP	0	Significant decrease in OI. Significant increase in $P_{(A\text{-}a)O_2}$ and SAP.
Goldman[70]	1997	Retrospective review study	None	30	20	$P_{(A\text{-}a)O_2}$, P_{aO_2}/F_{IO_2}, OI, acute lung injury score	60	Significant association between early-response INO and patient outcome. All patients with OI change $< 15\%$ died.
Nakagawa[67]	1997	Prospective, clinical observation	None	15 (14 patients)	10–80	OI, PVR, SVR, PAP, hypoxemia score, INO dose	38	Significant increase in OI. Significant decrease in PAP. Maximum beneficial dose 20–40 ppm. Decrease in PVR.
Okamoto[69]	1998	Open, non-randomized, dose-response	None	7	0.13–16	P_{aO_2}/F_{IO_2}, P_{aCO_2}, INO dose	57	INO significantly increased P_{aO_2}/F_{IO_2}. Optimal INO dose found to be <4 ppm. Slight decrease in P_{aCO_2}.
Sheridan[68]	1999	Open, non-randomized	None	11	5 or 10	P_{aO_2}/F_{IO_2}, P_{aO_2}	27	Significant improvement in P_{aO_2}/F_{IO_2}. Improvement in oxygenation (P_{aO_2} and S_{pO_2}) was immediate.

INO = inhaled nitric oxide
ARDS = acute respiratory distress syndrome
OI = oxygenation index
P_{aO_2}/F_{IO_2} = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen
$P_{(A\text{-}a)O_2}$ = alveolar-arterial oxygen difference
$\dot{Q}_S/\dot{Q}_T$ = shunt fraction
SAP = systemic arterial pressure
PAP = pulmonary artery pressure
CO = cardiac output
PVR = pulmonary vascular resistance
SVR = systemic vascular resistance
S_{pO_2} = blood oxygen saturation measured via pulse oximetry

of 20%, versus a 9% increase at 20 min in the placebo group ($p = 0.008$). Among the patients who emerged from cardiopulmonary bypass without pulmonary hypertension, there was no statistical difference. Russell et al concluded that INO is effective in treating pulmonary hypertension immediately after congenital heart surgery.

In a similar study Day et al sought to determine if INO was effective in decreasing PHTC after surgery for congenital heart defect.[76] Forty patients with PAP $\geq$ 50% of systemic arterial pressure after cardiopulmonary bypass were randomized to either 20 ppm INO ($n = 20$) or conventional therapy with nitrogen as placebo gas ($n = 20$). PHTC was defined as an acute episode of suprasystemic PAP associated with vital sign changes (blood pressure, heart rate) or oxygenation status that required a change in medical therapy or ventilatory support. Control patients that experienced PHTC were allowed to cross over to INO after failing conventional therapy. Each group enrolled 19 different patients. There were no significant differences in baseline hemodynamic values between the groups. At 1 hour after the initiation of INO there were significant changes ($p < 0.05$) in heart rate, PAP, left atrial pressure, pH, P_{aCO_2}, and P_{aO_2}/F_{IO_2}, but there were no differences between the groups after 1 hour. There was no difference in the rate of PHTC between the groups (4 control, 3 INO). In the 4 control patients who suffered PHTC there were

significant changes in heart rate, PAP, and P_{aO_2}/F_{IO_2} 1 hour after crossing over to INO. The authors concluded that INO did not significantly improve hemodynamics or arterial blood gases or reduce the incidence of PHTC, compared to conventional therapy.

In a recent study by Morris et al the investigators sought to determine if alkalosis or INO was more effective in reducing PAP or PVR in children with pulmonary hypertension after surgery for congenital heart defect.[77] This prospective, randomized, cross-over study enrolled 12 children with mean PAP > 25 mm Hg. Patients were randomized to receive INO (at 5 ppm for 15 min, then 40 ppm for 15 min) or hyperventilation (pH > 7.5 for 30 min), and the effects on hemodynamic variables were measured. After a 30-min washout period patients were randomized to the other treatment arm and measurements were repeated. After crossing over, all patients received both treatments in combination for 30 min. The hyperventilation group showed significant decreases in cardiac index, mean central venous pressure, mean PAP, and mean PVR, and an increase in SVR, and a small increase in oxygen extraction. The INO group showed significant decreases in heart rate, mean PAP, and PVR. There were no differences in response between 5 and 40 ppm INO. No rebound pulmonary hypertension was observed after gas discontinuation. Combination therapy (INO plus hyperventilation) decreased PVR and increased SVR. A further reduction in PAP was seen, without a change in PVR. The authors concluded that both INO and hyperventilation were effective in reducing PAP and PVR in children with pulmonary hypertension after cardiac surgery. INO may offer an overall advantage over hyperventilation with regard to pulmonary circulation, because hyperventilation causes undesirable changes in cardiac output (decrease) and SVR (increase).

In a double-blind study Miller et al randomized 124 patients to receive INO ($n = 63$) or placebo ($n = 61$) to investigate the role of selective pulmonary hypertension after congenital heart surgery in children.[78] Study gas was administered (10 ppm INO or placebo nitrogen) from after cardiopulmonary bypass until just prior to extubation. Among patients receiving INO significant differences were realized in PHTC (INO = 4, placebo = 7, relative risk unadjusted $p < 0.001$), shorter duration of mechanical ventilation (INO = 80 h, placebo = 112 h, $p = 0.019$), and total time on study gas (INO = 87 h, placebo = 117 h, $p = 0.023$). The authors concluded that the routine use of INO after congenital heart surgery could lessen the risk of PHTC and shorten the postoperative course, with no toxic effects.

In summary, a number of clinical trials and case reports suggest that INO is useful in the postoperative management of a critical rise in PAP.[72–75] In a study by Goldman et al INO was shown to be more effective than conventional management (intravenous prostacyclin) in lowering PAP.[79] PHTC is a significant complication and risk factor for children who have undergone congenital cardiac surgeries. Recent studies offer conflicting data on the therapeutic potential of INO for routine management of PHTC.[76–78] The use of INO for pediatric cardiac surgery patients appears to have some potential and beneficial effects but may or may not be more beneficial or cost-effective than conventional management strategies. Table 9 summarizes clinical trials of INO for pediatric congenital heart diseases.

Delivery Mechanisms

The indications for INO state:

> INO_{max}, in conjunction with *ventilatory support* and other appropriate agents is indicated for the treatment of term and near-term (> 34 wk) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for ECMO."[80]

Although most of the patients in the studies discussed above were intubated and required phasic MV, the ideal INO delivery mechanism should be usable with either phasic ventilators or continuous flow ventilators. INO occasionally needs to be delivered to nonintubated patients and can be administered via tight-fitting face mask,[81] transtracheal oxygen catheter,[82,83] nasal cannula,[84] or oxygen hood.[85]

Summary of Inhaled Nitric Oxide

Overall, INO offers a treatment for various disorders of neonates. INO appears most likely to benefit premature neonates who are hypoxemic despite mechanical support and high F_{IO_2}. Clinical trials indicate that among infants suffering PPHN, INO strongly reduces the need for ECMO or other invasive treatments. Data analysis suggests that a 20 ppm INO starting dose is most effective, and that doses > 40 ppm offer no additional clinical advantage. With patients who respond to INO, the typical duration of therapy appears to be < 7 days.

Several approaches to weaning INO have been successful, but caregivers must avoid abrupt discontinuation of INO. Ventilatory management remains important when parenchymal lung disease accompanies PPHN. In many studies the combination of HFOV (to optimize lung recruitment) and INO has shown greater benefit than either

Table 9. Summary of Clinical Trials of Inhaled Nitric Oxide for Pediatric Congenital Heart Diseases

First Author	Year	Design	Control	*n*	INO	Outcome Variables	Outcome
Curran[74]	1995	Open-label, nonrandomized	None	5* 15†	20, 40, 80	PAP, PVR, CO	Significant decrease in mean PAP
Day[76]	2000	Randomized, controlled, double-blind	Placebo	40 (38 patients)	20	PHTC, heart rate, PAP, LAP, pH, P_{aCO_2}, and P_{aO_2}/F_{IO_2}	Significant difference in heart rate, PAP, LAP, pH, P_{aCO_2}, and P_{aO_2}/F_{IO_2}
Journois[73]	1994	Open-label, nonrandomized	None	17	20–80	PAP, SAP, S_{aO_2}, $S_{\bar{v}O_2}$, CVP, LAP, urine output, ABG and VBG values	Significant decrease in PAP. Significant decreases in S_{aO_2} and $S_{\bar{v}O_2}$.
Miller[72]	1994	Prospective, open-label	None	13 (10 patients)	2, 10, or 20	PAP, PVR, SVR, PVR/SVR	Significant decrease in PAP and PVR. No difference in SVR. Initial PVR/SVR correlated with maximum pulmonary vasodilation response.
Miller[78]	2000	Randomized, controlled, double-blind	Placebo	124	10	PHTC, MV days, study gas time	Significant differences in PHTC. Significantly shorter MV days and study gas time
Morris[77]	2000	Prospective, randomized, crossover design	Hyper-ventilation	12	5‡ 40‡	CI, mean CVP, mean PAP, mean PVR, SVR, oxygen extraction.	*Hyperventilation:* Significant decreases in CI, mean CVP, mean PAP, mean PVR. Significant increases in SVR and oxygen extraction. *INO:* Significant decreases in heart rate, mean PAP, and PVR. No difference in INO dose. *Combination therapy:* Significant decrease in PVR and increase in SVR.
Russell[75]	1998	Randomized, controlled, double-blind	Placebo	40 (39 patients)	80	PAP, SAP	Significant decrease in PAP

INO = inhaled nitric oxide
*Atrioventricular canal
†Refractory postoperative pulmonary hypertension
PAP = pulmonary artery pressure
PVR = pulmonary vascular resistance
CO = cardiac output
PHTC = pulmonary hypertensive crisis
LAP = left arterial pressure
P_{aO_2}/F_{IO_2} = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen
SAP = systemic arterial pressure
S_{aO_2} = arterial oxygen saturation
$S_{\bar{v}O_2}$ = venous oxygen saturation
CVP = central venous pressure
ABG = arterial blood gas
VBG = venous blood gas
SVR = systemic vascular resistance
MV = mechanical ventilation
I = cardiac index
‡Sequentially administered for 15 min with a 30-min separation

therapy alone. Minimizing the toxicities of INO requires understanding the nuances of INO monitoring and infant care.

Multiple clinical trials suggest that neonates with CDH are unlikely to benefit from INO therapy. Data suggest a possible role for INO with preterm infants suffering hypoxemic respiratory failure and infants with CLD, but additional randomized, controlled studies are needed. For pediatric ARDS and congenital heart defect pulmonary hypertension, INO appears to be effective in improving oxygenation and reducing PVR, but the effects in the pediatric population appear to be of short duration (48–72 h). Though INO appears to offer rapid improvement of oxygenation and PVR, sustained or prolonged effects are questionable.

Carbon Dioxide and Hypoxic Gas Therapy

Introduction

The last 2 specialty gases to be reviewed are used, independent of one another, to treat a common congenital heart defect. Hypoplastic left heart syndrome (HLHS) is common among congenital heart defects, constituting 10% of all congenital heart defects. The incidence is 0.16–0.36 per 1,000 live births.[86] HLHS is more common in boys (55–70% male predominance).[87] HLHS includes a variety of cardiac malformations and is characterized by marked hypoplasia of the left ventricle and ascending aorta, and stenosis or atresia of the aortic and mitral valves. Coarctation of the aorta commonly coexists. The ventricular septum is usually intact.[88]

For many years no treatment was effective for this condition, and 90% of infants with this condition died by 1 month of age. Along with palliative care, there are now 2 surgical options (Norwood procedure and orthotopic heart transplant) that may improve survival of HLHS infants. Successful operative treatment is critically dependent on appropriate preoperative management. The first step in preoperative management is to maintain an intracardiac mixing of systemic and pulmonary blood flow. All patients with HLHS should be started on prostaglandin, 0.05–0.10 μg/kg/min, to maintain ductal patency and improve systemic blood flow. If a patent ductus arteriosus cannot be maintained, a balloon septostomy may be performed to artificially create a mixing lesion.

The next step of preoperative management requires equal balancing of systemic and pulmonary blood flow. Infants with HLHS have a complex cardiovascular physiology. Completely saturated pulmonary venous blood that returns to the left atrium cannot flow into the left ventricle because of a defective mitral valve (atresia, hypoplasia, or stenosis). This results in mixing of pulmonary and systemic venous blood in the right atrium, via an atrial septal defect, patent foramen ovale, or a large patent ductus arteriosus, causing systemic desaturation. Intracardiac mixing results in the right ventricle pumping this mixed blood to both the pulmonary and systemic circulations. Therefore blood exiting the right ventricle must flow either (1) via the branch pulmonary arteries to the lungs or (2) via the ductus arteriosus and descending aorta to the body. The volume of blood flow through either route of circulation is dependent on the resistance in each circuit due to PVR or SVR.

Blood flow is inversely proportional to resistance (the Ohm law); that is, when resistance in blood vessels decreases, blood flow through these vessels increases.[89] Following birth, in an HLHS infant, circumstances that result in an overall decrease in PVR result in a greater percentage of the right ventricular output being shunted to the lungs. This increase in pulmonary blood flow results in higher oxygen saturations and thus decreases systemic blood flow to the rest of the body. This ultimately results in poor perfusion and an increased likelihood of metabolic acidosis and oliguria. Coronary artery and cerebral perfusion are also dependent on systemic blood flow through the ductus arteriosus. Increased pulmonary blood flow therefore results in decreased flow to the coronary arteries and brain, with a risk of myocardial or cerebral ischemia.

Alternatively, if PVR increases to pressures substantially greater than SVR, blood flow is directed to the systemic circulation at the expense of pulmonary blood flow. This may result in profound hypoxemia. This unique cardiovascular physiology is dependent on SVR and PVR being carefully manipulated to achieve a balanced circulation with adequate systemic oxygenation. Using a mathematical model, Barnea et al studied the effects of the ratio of pulmonary to systemic blood flow ($\dot{Q}_P/\dot{Q}_S$) on systemic oxygen availability. They developed an equation derived from the key related variables: cardiac output, pulmonary venous oxygen saturation, and $\dot{Q}_P/\dot{Q}_S$. Barnea et al concluded that their mathematical model provided a theoretical basis for balancing pulmonary and systemic circulation and suggested that evaluating both systemic arterial and venous oxygen saturation may be useful to determine the relative pulmonary and systemic flows.[90] A mathematical model study by Austin et al[91] suggested that a $\dot{Q}_P/\dot{Q}_S$ of 1 would provide the largest safety margin with either low pulmonary oxygen conditions or decreased cardiac output.

Pulmonary blood flow should be limited; this is accomplished by avoiding excessive P_{aO_2}. Occasionally the infant is capable of performing this distribution of blood flow naturally, but frequently artificial manipulation of the PVR and SVR is needed to achieve and maintain this critical balance of blood flow. This artificial manipulation of the PVR is often where the respiratory therapist is asked to play a vital role in managing an HLHS child. Frequently intubation and mechanical ventilation are required because of apneas associated with the use of prostaglandins; if at all possible, the infant should be ventilated with room air. When mechanical ventilation at minimal ventilator settings and F_{IO_2} are not successful in manipulating the PVR, other ventilator strategies may be employed. The infant's PVR can be manipulated by specialty gases in one of 2 ways.[86,92] A review of the literature indicates that the 2 specialty gas strategies aimed at reducing PVR in HLHS infants are (1) artificial addition of carbon dioxide and (2) introduction of a hypoxic gas mixture (ie, a gas that has $<$ 21% oxygen) during mechanical ventilation.

Carbon Dioxide

Increasing the CO_2 level can be accomplished by mechanical ventilation with hypoventilation and/or sedation. Decreases in tidal volume, respiratory rate, or both to achieve hypoventilation and alkalosis frequently result in arterial desaturation. Jobes et al hypothesized that arterial desaturation occurs because of decreased functional residual capacity, closure of small airways, atelectasis, or hypoxemia.[93] This resulted in a different approach to initiating respiratory alkalosis through artificial means.

The earliest report of a specialty gas being used in the management of HLHS is with CO_2. In a small clinical trial Morray et al suggested that introducing small amounts of inspired CO_2 before and after surgery was an effective means to limit pulmonary blood flow by increasing PVR.[94] Elevating P_{aCO_2} into the range of 45–50 mm Hg can increase PVR.[93,95]

Carbon Dioxide Delivery Systems

The percentage of CO_2 in room air is approximately 0.03% or 0.22 mm Hg. The therapeutic range of CO_2 to be delivered is generally 1–4% or 8–30 mm Hg. Hoffman et al described an inexpensive system to titrate CO_2 through a blender and to the mechanically ventilated patient.[96] The system permitted easy normalization of pH and P_{aCO_2}, without a change in F_{IO_2}. In a later publication, Chatburn and Anderson described a double-blender mechanism to deliver controlled amounts of CO_2 and oxygen during mechanical ventilation.[97] They discovered that systematic adjustments were not predicted or straightforward, because blender calibrations do not hold for alternative gas mixtures. Chatburn and Anderson developed and tested a predictive nomogram that provides a quick and accurate way to predict the blender settings required to deliver precise concentrations of both oxygen and CO_2 through a double-blender system.

Hypoxic Gas Mixtures

The second method of increasing PVR with a specialty gas mixture is by decreasing P_{aO_2} to achieve $S_{aO_2} < 80\%$. Mechanical ventilation and an F_{IO_2} of 0.21 coupled with the various defects of HLHS typically accomplish this state of hypoxic pulmonary vasoconstriction or "clinical desaturation." For cases in which an infant continues to have a high S_{aO_2}, resulting in decreased PVR and shunting of blood toward the pulmonary system and away from the systemic circulation, the addition of nitrogen gas to the inspired gas (which has the ambient 21% oxygen) via the endotracheal tube or hood results in a hypoxic (ie, < 21% oxygen) gas mixture.[98,99] This use of a specialty gas (nitrogen) is commonly referred to as hypoxic gas therapy or subambient oxygen therapy.

Riordan et al investigated physiologic effects of respiratory manipulations in an animal model with a univentricular heart.[92] They sought to determine the effects on decreasing $\dot{Q}_P/\dot{Q}_S$ with common ventilatory treatments, adding positive end-expiratory pressure, altering inspired oxygen tension, and adding CO_2 to the ventilatory circuit. The authors concluded that the animal model demonstrated the value of estimating $\dot{Q}_P/\dot{Q}_S$ before initiating therapy. When the initial $\dot{Q}_P/\dot{Q}_S$ was greater than about 0.7, interventions that decreased $\dot{Q}_P/\dot{Q}_S$ increased oxygen delivery and were beneficial. The addition of CO_2 decreased $\dot{Q}_P/\dot{Q}_S$ and increased PVR, but to achieve statistically significant changes in $\dot{Q}_P/\dot{Q}_S$ and PVR required high concentrations of supplemental CO_2 (P_{aCO_2} 80–95 mm Hg, mean pH = 6.83 ± 0.12). Similar but lesser effects were seen with CO_2 concentrations similar to those used clinically (P_{aCO_2} 50–60 mm Hg, mean pH = 6.99 ± 0.11). These concentrations caused nonsignificant decrease in $\dot{Q}_P/\dot{Q}_S$ and nonsignificant increase in PVR. The different results seen with high and low CO_2 concentrations suggest that the effects of supplemental CO_2 are dose-dependent.

However, Riordan et al had a different result with lowering the inspired oxygen concentration.[92] As F_{IO_2} was lowered, the $\dot{Q}_P/\dot{Q}_S$ significantly decreased ($p < 0.05$), which appeared to be related to the action of lower F_{IO_2} on increasing PVR ($p < 0.05$). Although SVR appeared to decrease somewhat as F_{IO_2} was lowered, the change was not statistically significant.

Typically, F_{IO_2} of 0.15–0.21 has been used to manipulate PVR in children with HLHS. During administration of a hypoxic gas mixture, continuous monitoring of oxygen saturation, arterial blood gases, and F_{IO_2} is paramount to ensuring adequate $\dot{Q}_P/\dot{Q}_S$ and patient safety.

Hypoxic Gas Mixture Delivery Systems

In performing a literature review on the use of hypoxic gas mixtures, very little evidence was uncovered regarding the technical description of the delivery system. The traditional method of delivering hypoxic gas mixtures to mechanically ventilated patients has been to bleed a low flow of nitrogen into the ventilator circuit. This method often requires various flow rates to achieve oxygen dilution, so hypoxic gas mixtures are ordered as F_{IO_2} values or based on other measured and monitored clinical variables. Thus, the ability to accurately monitor those variables is vitally important.

Hypoxic gas (F_{IO_2} 0.15–0.21) is easily obtained via nitrogen dilution; however, the ability of standard, commercially available oxygen analyzers to accurately monitor low oxygen concentrations had not been well documented until recently. Myers and Chatburn conducted a bench test to assess the ability of 2 oxygen analyzers to provide accurate and reliable measurements of oxygen levels in hypoxic gas.[100] The 2 oxygen analyzers tested met the manufacturers' specifications of maximum error, which was easily maintained down to zero percent oxygen. Myers and Chatburn point out the important clinical issue of patient safety as it relates to the establishment of oxygen analyzer alarm limits when administering hypoxic gas.

The issue of monitoring patient safety and the requirement of establishing oxygen analyzer alarm limits are highly important when using the nitrogen bleed-in method of hypoxic gas delivery. Frequently the nitrogen flow rate is relatively low, and can be as low as 0.1 L/min when using time-cycled, pressure-limited ventilation to deliver F_{IO_2} of 0.19–0.20. However, this also indicates that flows as low as 0.1 L/min can change the oxygen concentration by 2–3%. This can result in potentially catastrophic incidents if the liter flow is inadvertently bumped, by even a fractional liter flow amount.

In a bench study by Dolcini et al, the investigators evaluated the feasibility of delivering hypoxic gas through a ventilator blender.[101] Specifically, they sought to determine the relationship between blender readings and delivered oxygen concentrations when the blender was supplied with nitrogen and air instead of oxygen and air. A size K cylinder of nitrogen (50 psi) was attached to each air inlet, and air (50 psi) was attached to each oxygen inlet, of 3 different infant ventilators (Infant Star, Bear Cub, and Bird VIP). Simulated ventilation, with settings that created a mean airway pressure of 11–12 cm H_2O, was delivered to a test lung. An analyzer was placed in-line before the humidifier. The ventilator blenders were adjusted to achieve the desired (ie, measured) oxygen concentrations of 0–21%. The authors concluded that hypoxic gas delivery can be achieved during mechanical ventilation by connecting the blender to nitrogen and air sources instead of oxygen and air. The maximum difference between the predicted setting and the actual setting on an individual ventilator was 5% with the Infant Star, and 2% with the other ventilators (Fig. 1). The difficulty with this proposed setup arises when the infant requires an $F_{IO_2} > 0.21$. With this setup the practitioner would be required to change high-pressure hoses and connections to the ventilator. This limitation led to the development (at Rainbow Babies and Children's Hospital, Cleveland, Ohio) of a mechanism to blend 3 sources of gas through a mechanical ventilator, which obviates changing the high-pressure hose (unpublished data). A 3-gas-source blending mechanism was designed to enable the practitioner to select an F_{IO_2} of 15–100%, in a matter of seconds (Fig. 2).

Some HLHS children require mechanical ventilation strictly for the precise delivery of hypoxic gas. Theoretically, mechanical ventilation could be avoided by administering subambient oxygen with a hood setup. This system (see Fig. 2) was tested in a study by Dolcini et al[102] to compare the efficacy of delivering hypoxic gas concentrations via a high-pressure system (Fig. 3) versus a traditional bleed-in system in an oxygen hood. An infant resuscitation manikin was placed in an oxygen hood for a simulation. Oxygen was simultaneously measured at 5 sites inside the hood. Blender flow was set at a standardized rate of 12 L/min. F_{IO_2} was decreased in increments of 1–4% (eg, 21% to 17% = 4% change). Time (in seconds) was recorded from stability of the pre-humidifier oxygen analyzer to a steady state of the other analyzers or a maximum time of 10 minutes as a test stop point. The bleed-in system was terminated by the time constraint in 79% (57 of 72) of the measurements, and in 77% (14 of the 18) of the measurements made at mouth level. The high-pressure system was terminated in 11% (8 of 72) of the measurements and in 0% (0 of 18) of the measurements made at mouth level. When subambient oxygen was analyzed at mouth level, the high-pressure system on average was 4.75 min faster to stability. The authors concluded that hypoxic gas delivery with a high-pressure system resulted in quicker stabilization to target F_{IO_2} than a traditional bleed-in method.

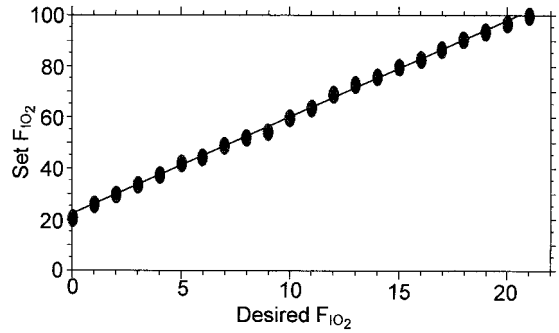

Fig. 1. Graph of the regression analysis, showing the maximum difference between predicted and actual fraction of inspired oxygen (F_{IO_2}) setting ($r^2 = 0.999$). If set F_{IO_2} is expressed as a percentage, then set $F_{IO_2} = 22.403 + (3.78 \times \text{set } F_{IO_2})$. (From Reference 101)

Summary of Carbon Dioxide and Hypoxic Gas Therapy

The purpose of this section was not to promote the use of supplemental gases or a specific delivery system for managing HLHS, but only to describe the clinical evidence about that use. The use of hypoxic gas and CO_2 for managing HLHS is somewhat controversial in many parts of the country. Hypoxic gas and CO_2 have proven clinically beneficial in optimizing intracardiac shunting by increasing PVR. However, many pediatric cardiac centers refrain from the use of these supplemental gases with HLHS infants and yet also achieve good clinical outcomes.

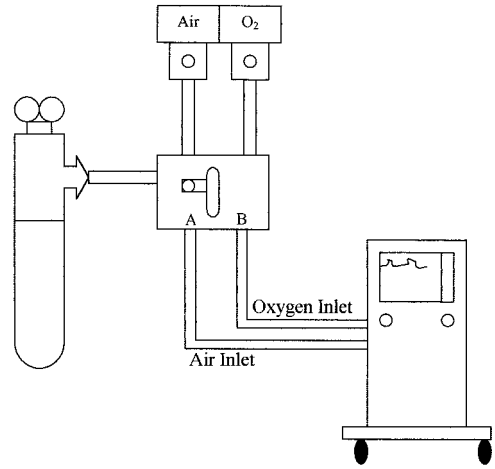

Fig. 2. A 3-gas-source blending mechanism for mechanical ventilators, designed at Rainbow Babies and Children's Hospital, Cleveland, Ohio, to blend air and oxygen or air and nitrogen.

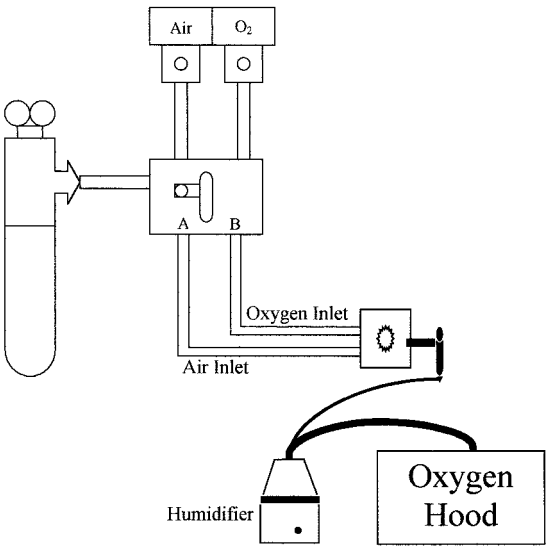

Fig. 3. A 3-gas-source blending mechanism for oxygen hoods, designed at Rainbow Babies and Children's Hospital, Cleveland, Ohio, to blend air and oxygen or air and nitrogen.

Summary

Research and controversy continue regarding the value of heliox, nitric oxide, hypoxic gas, and carbon dioxide for the treatment of certain cardiorespiratory disorders.

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Discussion

Salyer: One of my problems as a manager of respiratory therapists is the not-infrequent occurrence when a therapist is called on to set up an unusual application of equipment and they find the subambient oxygen setup is not put together properly. We've had more trouble with that than we should have. I'm curious about how many therapists you have doing this, how often you do it, and do you run into application errors because it's an unusual application that is used infrequently?

Myers: Good question. One cardiothoracic surgeon at my institution preferred the CO_2 bleed-in system, whereas the previous surgeon had preferred the nitrogen bleed-in system. Our current surgeon believes in neither system, so he hasn't asked for either one of them. But when we were administering hypoxic gases we were having long delays in getting the equipment set up, so we standardized it; we had it set up in one area of our department. Everything was all hooked up. All we had to do was roll it up to the bedside for the bleed-in method. We had no errors in getting the equipment or setting it up with a staff of about 20 people. The difficulty we had was that the equipment would get bumped (especially during respiratory isolation times, when staff would sometimes hang gowns over tanks or flow meters), causing important changes in F_{IO_2}. So that's why we adopted a flip switch mechanism. The biggest problem we had, with probably 4 or 5 patients we used it with, was the fact that someone would walk in and see the blender set at 86%, which was delivering about 16% oxygen, and they would want to turn it down. So we had to put a sign on the blender asking people not to touch it. The system with the hood is being used by one of Ric Rodriguez's colleagues, Dr Martin, to test how infants respond to hypoxic gas and desaturations. So it's still being used in a research setting, and it is very quick and reliable.

Cheifetz: I want to comment about safety. I always worry when a clinician varies the different gas mixtures administered through a ventilator, such as administering nitrogen and compressed air instead of oxygen and compressed air. There are important safety concerns because the F_{IO_2} control knob may not indicate the actual F_{IO_2} being delivered. A respiratory therapist or physician might look at the ventilator and say, "What are they doing with the F_{IO_2} set at 86%?" and then decrease the F_{IO_2} control knob to 21%. In that case, you would have a patient who is receiving almost *no* oxygen. And, beyond that, it has never made a lot of sense to me to deliver subambient oxygen levels to infants with HLHS, because the bottom line for these babies is oxygen delivery. If you want to optimize oxygen delivery, why administer less F_{IO_2}, when delivering exogenous CO_2 can achieve the same $\dot{Q}_P/\dot{Q}_S$ with potentially improved oxygen delivery?[1–3]

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Myers: That's a great question. There are 3 schools of thought: those who don't believe in either, those who advocate CO_2 bleed-in, and those who believe in manipulating PVR strictly through nitrogen bleed-in. In my institution we've been through all 3 schools, with 3 different cardiothoracic surgeons, each believing in something different.

I agree with your safety concern. We ran these things for days to see if they would do anything to the ventilators, and they really had no impact on the ventilators, but we were very concerned about the possibility of someone turning the F_{IO_2} control knob. All these actually have separate analyzers. For the most part we use Mini Ox III analyzers in our neonatal ICU, but all the patients who receive *hypoxic* gas mixtures are monitored with a Teledyne analyzer, because most oxygen analyzers have a default low alarm setting of about 17–18% oxygen. Obviously, that does no good for a low alarm reading if you want a patient on 15% oxygen. We had to get a letter from Dr Kercsmar, our medical director, and from our cardiothoracic surgeon to be allowed to get the Teledyne low alarm limit taken off so we could adjust the low alarm limit to below 15%. So we have that back-up mechanism of an alarm going off. Alarms are on at 13%, even if we have a patient on 15%, and the analyzers all are mounted on top of the ventilators, and we put a "Do Not Touch" sign on the dials. Ric can tell you that he's not even allowed to touch the ventilators in the neonatal ICU.

Rodriguez: I commend you for advancing the technology for hypoxic gas delivery; however, since we're in the era of evidence-based medicine I would point out that none of these delivery systems or therapeutic interventions have been shown in randomized trial to be any better than conservative management. So even though a lot of people have jumped on the subambient oxygen bandwagon, there is no evidence that conservative management with prostaglandin is any better or worse. I would suggest that many times surgeons use their anecdotal and personal experience in choosing one over the other. The majority of these babies actually do very well without *any* of these interventions, and they bal-

ance themselves very nicely once they are on prostaglandins. The information you provided in your presentation doesn't mean that people should be using all these devices and try these interventions without further evaluation in properly designed clinical trials.

With regard to INO I would add a word of caution to those using INO in places where there is no close contact with ECMO centers. A modest or minimal response to INO should be interpreted with caution when considering discontinuing INO therapy. We've seen some babies in whom INO was started and then discontinued because of what was believed to be a lack or response, and some of those babies deteriorated very quickly. Once you start INO at a place where there is no ECMO center readily available, you should not discontinue INO just because you don't see a marked response. In my view it is safer to stop the gas once you have arrived at the ECMO center where you can begin ECMO if there is a severe decompensation.

Myers: I think your points are very valid. I tried to make this presentation evidence-based, but there are no clinical studies of CO_2 and nitrogen for HLHS, so, unfortunately, there's not a whole lot of evidence. Most of the evidence is anecdotal: "I've seen it once, I've done it once." Because of the lack of evidence it's important that we describe the ways these systems have been set up and discuss the safety concerns and the safest methods so we can move forward towards clinical trials.

Wagener: I would refer to heliox as a therapy looking for a disease and to infant pulmonary hypertension as a disease looking for a therapy. My question regarding heliox is whether there is a tendency for the helium and oxygen to separate in the tank?

Myers: I don't know if heliox separates in the tank, but once it comes out into the atmosphere, it will separate. Even oxygen separates from the other gases inside a hood,[1] so you get different oxygen levels inside the hood. If you're running 50% oxygen into the hood, you'll get different F_{IO_2} readings throughout the hood.

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1. Barnhart SL. Oxygen therapy. In: Barnhart SL, Czervinske MP, editors. Perinatal and pediatric respiratory care, 2nd ed. Philadelphia: WB Saunders; 2003:141–154.

Wagener: Differences in gas density have been used clinically, since oxygen is heavier and settles to the bottom. In a plastic-walled crib you can flow oxygen onto the bed surface and it will concentrate to as high as 30%.[1]

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Cheifetz: As far as I am aware, every time it has been investigated, the heliox delivered from the tank is not separated. The only separation, as far as I know, occurs after delivery. If it is administered to an oxygen hood, then separation will occur.

You didn't mention one point that I think is important to stress. It's true that there have been no large clinical studies with heliox (all of the data are from small studies or anecdotal reports), but, as far as I know, no adverse heliox effects have been reported. The studies either indicate that heliox works or that it does not have any effect. So with a critically ill patient with impending respiratory failure due to airway obstruction, it seems worthwhile to do a trial of heliox, since there are no adverse effects. Heliox is a relatively inexpensive therapy and it may prevent the need for intubation/reintubation or may shorten the course of mechanical ventilation.

Wiswell: Do you get informed consent, though? My basic problem is that it's not a uniformly accepted therapy, nor is it FDA approved. My concern would be not obtaining informed consent for an unapproved therapy.

Cheifetz: That is a good question. At Duke we do not obtain informed consent for the use of heliox for indications that are supported in the medical literature. We base our clinical decisions on the evidence that *is* available in the literature. Granted, there are no large-scale, randomized, controlled, clinical trials, but I believe there is adequate evidence to support the general clinical use of heliox at this point.

Wagener: I might say that the biggest risk is delay in doing what's proven therapy.

Myers: I think that, if nothing else, heliox is a very, very safe gas. Other than the vocal distortion it causes, there's never been any adverse effects identified, from short bursts or from days of administration.

Cheifetz: Helium is a completely inert gas. No one has ever demonstrated any adverse effects or biologic interactions associated with heliox.

Salyer: I would point out, as a manager responsible for developing safe systems, that there are some safety issues with administering heliox, just like there are safety issues with nitrogen and hypoxic gas. I agree it's a relatively small risk, but I don't think it's *completely* benign.

In the INO studies there was no difference in mortality between those who received INO and those who didn't, but the INO patients did not require ECMO as often. Did those studies indicate that there was no difference in mortality even *after* the patients went on ECMO? That is, though fewer INO patients needed ECMO, some of them went on ECMO. Does

the mortality rate you mentioned include the ECMO intervention? And if it does, why did they end up going on ECMO at all?

Wagener: It was an intent-to-treat study, so it includes patients who failed with INO and went on to ECMO.

Salyer: Right. So the mortality rates include those patients who actually ended up on ECMO. Do you see my question? If mortality is not different even among those who went on ECMO, I have to ask why they went on ECMO? Am I thinking about that wrong?

Wagener: Half the group were treated conventionally and half were treated initially with INO. Of both groups, a certain percentage progressed and needed ECMO. The conventionally treated group had a higher percentage progressing to ECMO than the group that was treated initially with INO. In the end, since this was an intent-to-treat protocol, you have to look at total overall mortality.

Salyer: But we can't tease out from those studies the effect of ECMO on mortality, because of the way they were structured?

Wiswell: I think the mortality rate among the kids who went on ECMO is essentially the same as among those who didn't go on ECMO, in both groups, whether they were on INO or ECMO. I think you're asking, "Well, ECMO's no good, so shouldn't we just use INO?" As you heard me say yesterday, I propose that ECMO's a proven therapy. Where all the kids started in the INO trials, on average they already meet ECMO criteria. My contention as a devil's advocate was, why should we use INO at all?