Inhaled Nitric Oxide Therapy

63

John P. Kinsella

I. Introduction
   A. Inhaled nitric oxide (iNO) therapy for the treatment of newborns with hypoxemic respiratory failure and pulmonary hypertension has dramatically changed management strategies for this critically ill population.
   B. iNO therapy causes potent, selective, and sustained pulmonary vasodilation and improves oxygenation in term newborns with severe hypoxemic respiratory failure and persistent pulmonary hypertension.
   C. Multicenter randomized clinical studies have demonstrated that iNO therapy reduces the need for extracorporeal membrane oxygenation (ECMO) treatment in term neonates with hypoxemic respiratory failure.
   D. The potential role of iNO in the preterm newborn is currently controversial and its use remains investigational in this population.

II. Rationale for iNO Therapy
   A. The physiologic rationale for iNO therapy in the treatment of neonatal hypoxemic respiratory failure is based upon its ability to achieve potent and sustained pulmonary vasodilation without decreasing systemic vascular tone.
   B. Persistent pulmonary hypertension of the newborn (PPHN) is a syndrome associated with diverse neonatal cardiac and pulmonary disorders that are characterized by high pulmonary vascular resistance (PVR) causing extrapulmonary right-to-left shunting of blood across the ductus arteriosus and/or foramen ovale (Chap. 72).
   C. Extrapulmonary shunting from high PVR in severe PPHN of the newborn can cause critical hypoxemia, which is poorly responsive to inspired oxygen or pharmacologic vasodilation.
   D. Historically, vasodilator drugs administered intravenously, such as tolazoline and sodium nitroprusside, were often unsuccessful because of systemic hypotension and an inability to achieve or sustain pulmonary vasodilation.
   E. The ability of iNO therapy to selectively lower PVR and decrease extrapulmonary venoarterial admixture accounts for the acute improvement in oxygenation observed in newborns with PPHN.

J.P. Kinsella, M.D. (✉)
Department of Pediatrics, Section of Neonatology, Pediatric Heart-Lung Center, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, CO, USA
e-mail: John.Kinsella@UCDenver.edu

S.M. Donn, S.K. Sinha (eds.), *Manual of Neonatal Respiratory Care*,
DOI 10.1007/978-3-319-39839-6_63

F. Oxygenation can also improve during iNO therapy in some newborns who do not have extrapulmonary right-to-left shunting. Hypoxemia in these cases is primarily the result of intrapulmonary shunting caused by continued perfusion of lung units that lack ventilation (e.g., atelectasis), with variable contributions from ventilation/perfusion (V/Q) inequality. Low dose iNO therapy can also improve oxygenation by re-directing blood from poorly aerated or diseased lung regions to better aerated distal air spaces ("microselective effect").

G. The clinical benefits of low dose iNO therapy may include reduced lung inflammation and edema, as well as potential protective effects on surfactant function, but these effects remain clinically unproven.

H. The diagnostic value of iNO therapy is also important, in that failure to respond to iNO raises important questions about the specific mechanism of hypoxemia. Poor responses to iNO should lead to further diagnostic evaluation for "unsuspected" anatomic cardiovascular or pulmonary disease.

III. Evaluation of the Term Newborn for iNO Therapy

A. The cyanotic newborn

1. History

a. Assess the primary cause of hypoxemia. Marked hypoxemia in the newborn can be caused by lung parenchymal disease with intrapulmonary shunting, pulmonary vascular disease causing extrapulmonary right-to-left shunting, or anatomic right-to-left shunting associated with congenital heart disease.

b. Assessment of risk factors for hypoxemic respiratory failure

(1) Prenatal ultrasound studies

(a) Lesions such as diaphragmatic hernia and congenital pulmonary airway malformation are frequently diagnosed prenatally.

(b) Although many anatomic congenital heart diseases can be diagnosed prenatally, vascular abnormalities (e.g., aortic coarctation, total anomalous pulmonary venous return) are more difficult to diagnose.

(c) A history of a structurally normal heart by fetal ultrasonography should be confirmed with echocardiography in the cyanotic newborn.

c. Maternal historical information

(1) History of severe and prolonged oligohydramnios causing pulmonary hypoplasia

(2) Prolonged fetal brady- and tachyarrhythmias and marked anemia (caused by hemolysis, twin-to-twin transfusion, or chronic hemorrhage) may cause congestive heart failure, pulmonary edema, and respiratory distress.

(3) Maternal illness (e.g., diabetes mellitus), medications (e.g., aspirin causing premature constriction of the ductus arteriosus), and drug use may contribute to disordered transition and cardiopulmonary distress in the newborn.

(4) Risk factors for infection causing sepsis/pneumonia should also be considered, including premature or prolonged rupture of membranes, fetal tachycardia, maternal leukocytosis, uterine tenderness, and other signs of intra-amniotic infection.

d. Events at delivery

(1) If positive pressure ventilation is required in the delivery room, the risk of pneumothorax increases.

(2) History of meconium-stained amniotic fluid, particularly if meconium is present below the vocal cords, should raise the suspicion of meconium aspiration syndrome (Chap. 71).

(3) Birth trauma (e.g., clavicular fracture and phrenic nerve injury) or acute feto-maternal/feto-placental hemorrhage may also cause respiratory distress in the newborn.

2. Physical examination
   a. The initial physical examination provides important clues to the etiology of cyanosis (Chap. 13).
   b. Marked respiratory distress in the newborn (retractions, grunting, and nasal flaring) suggests the presence of pulmonary parenchymal disease with decreased lung compliance.
   c. Recognize that airway disease (e.g., tracheo-bronchomalacia) and metabolic acidemia can also cause severe respiratory distress.
   d. In contrast, the newborn with cyanosis alone ("non-distressed tachypnea") typically has cyanotic congenital heart disease (e.g., transposition of the great vessels) or idiopathic PPHN.
3. Interpretation of pulse oximetry measurements
   a. Right-to-left shunting across the ductus arteriosus causes post-ductal desaturation.
   b. Interpretation of pre-ductal (right hand) and post-ductal (lower extremity) saturation by pulse oximetry provides important clues to the etiology of hypoxemia in the newborn.
   c. If the measurements of pre- and post-ductal SpO_2 are equivalent, this suggests either that the ductus arteriosus is patent and PVR is sub-systemic (i.e., the hypoxemia is caused by parenchymal lung disease with intrapulmonary shunting or cyanotic heart disease with ductal-dependent pulmonary blood flow), or that the ductus arteriosus is closed (precluding any interpretation of pulmonary artery pressure without echocardiography).
   d. It is exceptionally uncommon for the ductus arteriosus to close in the first hours of life in the presence of supra-systemic pulmonary artery pressures.
   e. When the post-ductal SpO_2 is lower than pre-ductal SpO_2 (>5 % gradient), the most common cause is supra-systemic PVR in PPHN, causing right-to-left shunting across the ductus arteriosus (associated with meconium aspiration syndrome, surfactant deficiency/dysfunction, congenital diaphragmatic hernia, pulmonary hypoplasia, or idiopathic).
   f. Ductal-dependent systemic blood flow lesions (hypoplastic left heart syndrome, critical aortic stenosis, interrupted aortic arch, and aortic coarctation) may also present with post-ductal desaturation.
   g. Anatomic pulmonary vascular disease (alveolar capillary dysplasia, pulmonary venous stenosis, and anomalous venous return with obstruction) can cause supra-systemic PVR with right-to-left shunting across the ductus arteriosus and post-ductal desaturation.
   h. The unusual occurrence of markedly lower pre-ductal SaO_2 compared to post-ductal measurements suggests one of two diagnoses: transposition of the great vessels with pulmonary hypertension, or transposition with coarctation of the aorta.
4. Laboratory and radiologic evaluation
   a. One of the most important tests to perform in the evaluation of the newborn with cyanosis is the chest radiograph (CXR).
   b. The CXR can demonstrate the classic findings of RDS (air bronchograms, diffuse granularity, and underinflation), meconium aspiration syndrome, or congenital diaphragmatic hernia.
   c. The important question to ask when viewing the CXR is whether the severity of hypoxemia is out of proportion to the radiographic changes. Marked hypoxemia despite supplemental oxygen in the absence of severe pulmonary parenchymal disease radiographically suggests the presence of an extrapulmonary right-to-left shunt (idiopathic PPHN of the newborn or cyanotic heart disease).

d. Other essential measurements include an arterial blood gas analysis, a complete blood count to evaluate for infection, and blood pressure measurements in the right arm and a lower extremity to determine aortic obstruction (interrupted aortic arch, coarctation).

5. Response to supplemental oxygen (100 % oxygen by hood, mask, or endotracheal tube).
   a. Marked improvement in SpO_2 (increase to 100 %) with supplemental oxygen suggests an intrapulmonary shunt (lung disease) or reactive PPHN of the newborn from vasodilation.
   b. The response to mask CPAP is also a useful discriminator between severe lung disease and other causes of hypoxemia.
   c. Most patients with PPHN of the newborn have at least a transient improvement in oxygenation in response to interventions such as high inspired oxygen and/or mechanical ventilation. If the pre-ductal SpO_2 never reaches 100 %, the likelihood of cyanotic heart disease is high.
6. Echocardiography (Chap. 25).
   a. The definitive diagnosis in newborns with cyanosis and hypoxemic respiratory failure often requires echocardiography (Fig. 63.1).
   b. The initial echocardiographic evaluation is important to rule out structural heart disease causing hypoxemia.
   c. It is critically important to diagnose congenital heart lesions for which iNO treatment would be contraindicated.
   d. Congenital heart diseases that can present with hypoxemia unresponsive to high inspired oxygen concentrations (e.g., dependent upon right-to-left shunting across the ductus arteriosus) include critical aortic stenosis and coarctation, interrupted aortic arch, and hypoplastic left heart syndrome. Decreasing PVR with iNO in these conditions could lead to systemic hypoperfusion and delay definitive diagnosis.
   e. PPHN of the newborn is defined by the echocardiographic determination of extrapulmonary veno-arterial admixture (right-to-left shunting at the foramen ovale and/or ductus arteriosus), not simply evidence of increased PVR.

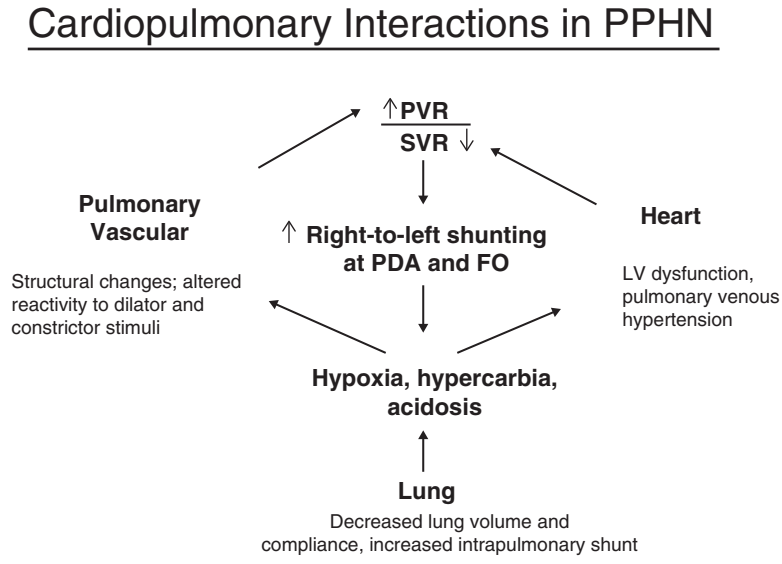

Fig. 63.1 Cardiopulmonary interactions in persistent pulmonary hypertension of the newborn

f. Doppler assessments of atrial and ductal level shunts provide essential information when managing a newborn with hypoxemic respiratory failure.
g. Left-to-right shunting at the foramen ovale and ductus with marked hypoxemia suggests predominant intrapulmonary shunting, and interventions should be directed at optimizing lung inflation.
h. In the presence of severe left ventricular dysfunction and pulmonary hypertension, pulmonary vasodilation alone may be ineffective in improving oxygenation. The echocardiographic findings in this setting include right-to-left ductal shunting (caused by supra-systemic PVR), and mitral insufficiency with *left-to-right* atrial shunting.

IV. Candidates for iNO Therapy
A. Several pathophysiologic disturbances contribute to hypoxemia in the newborn infant, including cardiac dysfunction, airway and pulmonary parenchymal abnormalities, and pulmonary vascular disorders.
1. In some newborns with hypoxemic respiratory failure, a single mechanism predominates (e.g., extrapulmonary right-to-left shunting in idiopathic PPHN), but more commonly, several of these mechanisms contribute to hypoxemia.
2. MAS has complicated cardiopulmonary pathophysiology. Meconium may obstruct some airways decreasing V/Q ratios and increasing intrapulmonary shunting. Other lung segments may be overventilated relative to perfusion and cause increased physiologic dead space. Moreover, the same patient may have severe pulmonary hypertension with extrapulmonary right-to-left shunting at the ductus arteriosus and foramen ovale, and LV dysfunction.
3. The effects of iNO may be suboptimal when lung volume is decreased in association with pulmonary parenchymal disease. Atelectasis and air space disease (pneumonia, pulmonary edema) will decrease effective delivery of iNO to its site of action in terminal lung units.
4. The effects of inhaled NO on ventilation–perfusion matching appear to be optimal at low doses (<20 ppm).
5. In cases complicated by homogeneous (diffuse) parenchymal lung disease and underinflation, pulmonary hypertension may be exacerbated because of the adverse mechanical effects of underinflation on PVR. In this setting, effective treatment of the underlying lung disease is essential (and sometimes sufficient) to cause resolution of the accompanying pulmonary hypertension.

B. Clinical criteria
1. Gestational and postnatal age
a. Available evidence from clinical trials supports the use of iNO in late preterm (>34 weeks' gestation) and term newborns.
b. Clinical trials of iNO in the newborn have incorporated ECMO treatment as an endpoint. Therefore, most patients have been enrolled in the first few days of life.
c. Although one of the pivotal studies used to support FDA approval of iNO therapy included as an entry criterion a postnatal age up to 14 days, the average age at enrollment in that study was 1.7 days.
d. Currently, clinical trials support the use of iNO before treatment with ECMO, usually within the first week of life.
e. Clinical experience suggests that iNO may be of benefit as an adjuvant treatment after ECMO therapy in patients with sustained pulmonary hypertension (e.g., congenital diaphragmatic hernia). Postnatal age alone should not define the duration of therapy in cases where prolonged treatment could be beneficial.

C. Severity of illness
   1. Studies support the use of iNO in infants who have hypoxemic respiratory failure with evidence of PPHN requiring mechanical ventilation and high inspired oxygen concentrations.
   2. The most common criterion employed has been the oxygenation index (OI Chap. 20). Although clinical trials commonly allowed for enrollment with OI >25, the mean level at study entry in multicenter trials approximated 40.
   3. There is no evidence that starting iNO therapy at a lower OI (i.e., <25) reduces the need for treatment with ECMO.
   4. Current multicenter studies suggest that indications for treatment with iNO may include an OI >25 with echocardiographic evidence of extrapulmonary right-to-left shunting.

V. Treatment Strategies
   A. Dose
      1. The first studies of iNO treatment in term newborns reported initial doses that ranged up to 80 ppm. Early laboratory and clinical studies established the boundaries of iNO dosing protocols for subsequent randomized, clinical trials in newborns.
      2. Recommended starting dose for iNO in the term newborn is 20 ppm.
      3. *Increasing the dose to 40 ppm does not generally improve oxygenation in patients who do not respond to the lower dose of 20 ppm.*
      4. Although brief exposures to higher doses (40–80 ppm) appear to be safe, *sustained treatment with 80 ppm NO increases the risk of methemoglobinemia.*
   B. Duration of treatment
      1. In multicenter, clinical trials, the typical duration of iNO treatment has been <5 days, which parallels the clinical resolution of PPHN.
      2. Individual exceptions occur, particularly in cases of pulmonary hypoplasia.
      3. If iNO is required for >5 days, investigations into other causes of pulmonary hypertension should be considered (e.g., alveolar capillary dysplasia), particularly if discontinuation of iNO results in supra-systemic elevations of pulmonary artery pressure by echocardiography.
      4. It is reasonable to discontinue iNO if the F_iO_2 is <0.60 and the PaO_2 is >60 without evidence of rebound pulmonary hypertension or an increase in $F_iO_2 > 15\%$ after iNO withdrawal.
   C. Weaning
      1. After improvement in oxygenation occurs with the onset of iNO therapy, strategies for weaning the iNO dose become important.
      2. Numerous approaches have been employed, and few differences have been noted until final discontinuation of iNO treatment.
      3. In one study, iNO was reduced from 20 to 6 ppm after 4 h of treatment without acute changes in oxygenation. In another trial, iNO was reduced in a stepwise fashion to as low as 1 ppm without changes in oxygenation.
   D. Monitoring
      1. Electrochemical devices accurately monitor NO and NO_2 levels.
      2. NO_2 levels remain low at delivered iNO doses within the recommended ranges.
      3. Methemoglobinemia occurs after exposure to high concentrations of iNO (80 ppm). This complication has not been reported at lower doses of iNO ($\leq$20 ppm).
      4. Because methemoglobin reductase deficiency may occur unpredictably, it is reasonable to measure methemoglobin levels by co-oximetry within 4 h of starting iNO therapy and subsequently at 24 h intervals.

E. Ventilator management
   1. Along with iNO treatment, other therapeutic strategies have emerged for the management of the term infant with hypoxemic respiratory failure.
   2. Considering the important role of parenchymal lung disease in specific disorders included in the syndrome of PPHN, pharmacologic pulmonary vasodilation alone should not be expected to cause sustained clinical improvement in many cases.
   3. Patients not responding to iNO can show marked improvement in oxygenation with adequate lung inflation alone.
   4. In newborns with severe lung disease, HFOV is frequently used to optimize lung inflation and minimize lung injury (Chap. 43).
   5. In clinical pilot studies using iNO, the combination of HFOV and iNO caused the greatest improvement in oxygenation in newborns who had severe pulmonary hypertension complicated by diffuse parenchymal lung disease and underinflation (e.g., RDS, pneumonia).
   6. A randomized, multicenter trial demonstrated that treatment with HFOV + iNO was often successful in patients who failed to respond to HFOV or iNO alone in severe pulmonary hypertension, and differences in responses were related to the specific disease associated with the various complex disorders.

VI. The Preterm Newborn
   A. Background
      1. The effectiveness of iNO in the late preterm and term newborn is largely from its properties as a selective pulmonary vasodilator; however, numerous laboratory studies also demonstrate other important effects, such as decreasing lung inflammation, reducing oxidant stress, and enhancing alveolarization and lung growth.
      2. These observations formed the basis for studying iNO in premature newborns at risk for developing bronchopulmonary dysplasia (BPD).
      3. Numerous randomized, controlled trials of iNO in premature newborns have been conducted over the last 2 decades. Meta-analyses of these studies reported no net improvement in either BPD or developmental sequelae. iNO therapy also was not associated with an increased risk of adverse events.
      4. The NIH Consensus Development Conference concluded that the use of iNO to prevent BPD is not supported by available evidence, and that "there are rare clinical situations, including pulmonary hypertension or hypoplasia, that have been inadequately studied in which iNO may have benefit in infants <34 weeks' gestation" and that "use in this population should be left to clinical discretion."
      5. Recent joint guidelines from the American Heart Association and American Thoracic Society supported the role of iNO in treating severe pulmonary hypertension in premature newborns.
   B. Current status of iNO treatment in premature newborns.
      1. Inhaled NO therapy should not be used in premature infants for the prevention of BPD, as multicenter studies have failed to consistently demonstrate efficacy for this purpose.
      2. Inhaled NO therapy can be beneficial for preterm infants with severe hypoxemia that is primarily from PPHN physiology rather than parenchymal lung disease, particularly if associated with prolonged rupture of membranes and oligohydramnios.
      3. Inhaled NO is preferred over other pulmonary vasodilators in preterm infants based on a strong safety signal from short- and long-term follow-up of large numbers of patients from multicenter randomized clinical trials for BPD prevention.

Suggested Reading

Abman SH, Hansmann G, Archer SL, et al. Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. Circulation. 2015;132:1–66.

Ballard RA, Truog WE, Cnaan A, et al. Inhaled nitric oxide in preterm infants undergoing mechanical ventilation. N Engl J Med. 2006;205:343–53.

Clark RH, Kueser TJ, Walker MW, et al. Low-dose inhaled nitric oxide treatment of persistent pulmonary hypertension of the newborn. N Engl J Med. 2000;342:469–74.

Cole FS, Alleyne C, Barks JD, et al. NIH consensus development conference statement: inhaled nitric-oxide therapy for premature infants. Pediatrics. 2011;127: 363–9.

Davidson D, Barefield ES, Kattwinkel J, et al. Safety of withdrawing inhaled nitric oxide therapy in persistent pulmonary hypertension. Pediatrics. 1999;104:231–6.

Gerlach H, Rossaint R, Pappert D, Falke KJ. Time-course and dose-response of nitric oxide inhalation for systemic oxygenation and pulmonary hypertension in patients with adult respiratory distress syndrome. Euro J Clin Invest. 1993;23:499–502.

Gersony WM. Neonatal pulmonary hypertension: pathophysiology, classification and etiology. Clin Perinatol. 1984; 11:517–24.

Hallman M. Molecular interactions between nitric oxide and lung surfactant. Biol Neonate. 1997;71:44–8.

Kinsella JP, Abman SH. Clinical approach to inhaled nitric oxide therapy in the newborn. J Pediatr. 2000;136:717–26.

Kinsella JP, Neish SR, Shaffer E, Abman SH. Low-dose inhalational nitric oxide in persistent pulmonary hypertension of the newborn. Lancet. 1992;340: 819–20.

Kinsella JP, Truog WE, Walsh WF, et al. Randomized, multicenter trial of inhaled nitric oxide and high frequency oscillatory ventilation in severe persistent pulmonary hypertension of the newborn. J Pediatr. 1997;131:55–62.

Kinsella JP, Walsh WF, Bose CL, et al. Inhaled nitric oxide in premature neonates with severe hypoxaemic respiratory failure: a randomised controlled trial. Lancet. 1999;354:1061–5.

Kinsella JP, Cutter GR, Walsh WF, et al. Early inhaled nitric oxide therapy in premature newborns with respiratory failure. N Engl J Med. 2006;205:354–64.

Kinsella JP, Steinhorn RH, Krishnan US, et al. Recommendations for the use of inhaled nitric oxide therapy in premature newborns with severe pulmonary hypertension. J Pediatr. 2015. doi:10.1016/j.jpeds.2015.11.050.

Levin DL, Heymann MA, Kitterman JA, et al. Persistent pulmonary hypertension of the newborn. J Pediatr. 1976;89:626.

Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. N Engl J Med. 1997;336:597–604.

Roberts JD, Polaner DM, Lang P, Zapol WM. Inhaled nitric oxide in persistent pulmonary hypertension of the newborn. Lancet. 1992;340:818–9.

Schreiber MD, Gin-Mestan K, Marks JD, et al. Inhaled nitric oxide in premature infants with the respiratory distress syndrome. N Engl J Med. 2003;349: 2099–107.

Wessel DL, Adatia I, Van Marter LJ, et al. Improved oxygenation in a randomized trial of inhaled nitric oxide for persistent pulmonary hypertension of the newborn. Pediatrics. 1997;100:e7.