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Inhaled Nitric Oxide in Infants and Children

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Endogenous nitric oxide (NO)[4, 8, 17, 23, 24, 29] has been identified as affecting endothelium-derived relaxing factor, which produces pulmonary vasodilation. Neonates, infants, and children may develop pulmonary hypertension that does not respond to endogenous NO; therefore, exogenous NO can be used to induce pulmonary vasodilation.

Causes of Pulmonary Hypertension

All infants are born with pulmonary hypertension. While in utero, the fetus receives oxygen from the mother via the placenta, with most blood being shunted away from the lungs by the foramen ovale and ductus arteriosus. Fetal systemic pressure is low and pulmonary pressure is high. When the newborn takes a first breath and the umbilical cord is cut, these formations begin to close. Normally during this process, high pulmonary pressures begin to decrease, while systemic pressures begin to increase. Persistent pulmonary hypertension of the newborn (PPHN) or persistent fetal circulation (PFC), a life-threatening condition, can result when this process does not take place.

Conditions associated with pulmonary hypertension in the newborn include meconium aspiration, respiratory distress syndrome, pneumonia, sepsis, pneumothorax, prematurity, and congenital diaphragmatic hernia. In some cases, the cause of pulmonary hypertension cannot be determined.[24] Anatomic differences in the lungs, such as hypertrophy or hyperplasia of the pulmonary smooth muscle, can also cause pulmonary hypertension. Patients with congenital diaphragmatic hernias may have hypoplasia of the lungs as well as problems with the system that regulates pulmonary vascular tone.[24] Preoperative or postoperative pulmonary hypertension seen in patients with congenital heart disease is linked to significant morbidity and mortality.[18, 25, 28]

Hageman et al[14] classified PPHN as either primary or secondary. Primary PPHN is caused by hypoxemia or acidemia, which alters the pulmonary vessels' ability to vasodilate. Secondary PPHN is defined as any condition that places the infant at risk for pulmonary vasoconstriction, such as meconium aspiration, pneumonia, sepsis, and congenital anomalies of the lung and airway. Death in the primary PPHN results from the inability to maintain adequate oxygenation. The outcome for infants with secondary

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PPHN depends on whether the severity of the underlying disease causes respiratory failure.

Treatments for Pulmonary Hypertension Before Nitric Oxide

PPHN can be treated using a variety of therapies aimed at decreasing the pulmonary hypertension and increasing oxygenation. Intubation and assisted ventilation are used to increase oxygenation to facilitate the end result of pulmonary artery vasodilation. Neuroblockade and sedation can be used to maximize ventilation. Patients on a mechanical ventilator can be hyperventilated to produce alkalosis. Sodium bicarbonate also can be infused to increase alkalization. This medication must be closely monitored, however, to prevent hypernatremia and increase serum osmolarity.[24, 26]

Dobutamine, tolazoline, and prostacycline are used to increase systemic pressure, while magnesium sulfate can dilate the vessels. Note that these vasodilators dilate the systemic vessels as well as the pulmonary arteries, which can cause systemic hypotension.[24]

In 1984, Hageman et al[14] reviewed charts of neonates in three neonatal intensive care units (NICUs) who had discharge diagnoses of PPHN. The most common treatments for PPHN during 1980 and 1981 were hyperventilation (HV) alone, or HV and tolazoline. Treatment with HV achieved a statistically significant survival rate.

Extracorporeal membrane oxygenation (ECMO) is a newer treatment modality that can be used after other treatments have been unsuccessful. Each institution that uses ECMO has specific criteria that must be met for an infant or child to be considered a candidate for the treatment.

ECMO is based on the principles of cardiopulmonary bypass (CPB), where blood is removed by a cannula and filtered through a machine that removes carbon dioxide and oxygenates the blood. The blood is returned to the patient through another cannula. ECMO requires surgical placement of the cannulae. The patient must be heparinized to prevent clotting, which presents a risk of intracranial hemorrhage or bleeding disorders.[24] ECMO is costly and requires specially trained staff and special equipment.

Use of Nitric Oxide

NO is a gas that has been found to be an effective pulmonary vasodilator without causing systemic vasodilation. Administered by inhalation, NO is short-acting (between 2 and 10 seconds) because it binds to hemoglobin, which inactivates it.[12, 26] NO is easy to administer and its cost is relatively low.[17]

NO is used in neonates, infants, and children with pulmonary hypertension who have not responded to conventional treatment. CPB may raise the pulmonary vascular resistance in children who have undergone open-heart surgery. Wessel et al[28] studied endothelial function following CPB and found that pulmonary endothelial dysfunction and pulmonary hypertension may be caused by CPB. Inhaled NO (INO) was used as a selective pulmonary vasodilator with pulmonary hypertension after CPB.

Adatia et al[1] described a diagnostic use for INO for neonates after cardiac surgery. After CPB, impairment of endothelium-dependent vascular relaxation can complicate the postoperative course by causing transient pulmonary hypertension.[28] To determine whether this is the result of an anatomic pulmonary blood flow obstruction or pulmonary vasoconstriction, Adatia studied 15 patients who developed postoperative pulmonary hypertension or excessive cyanosis by administering INO.[1] Nine of the neonates showed decreased pulmonary artery pressure and pulmonary vascular resistance. The remaining 6 did not respond to INO and had an anatomic obstruction to pulmonary blood flow. Therefore, postoperative patients who do not respond to INO should receive additional diagnostic tests, which may indicate the need for further surgery.

Jesse Roberts et al[23] studied the use of inhaled, low concentration of NO and oxygen in children with congenital heart defects undergoing cardiac catheterization. The patients were given 80 ppm NO and fraction of inspired oxygen (F_{IO_2}) 0.21 to 0.30, or F_{IO_2} 0.9.

Within 1 to 3 minutes, pulmonary vascular resistance and pulmonary artery pressure were decreased. When INO was stopped, pulmonary vascular resistance and pulmonary artery pressure returned to baseline readings. When F_{IO_2} 0.9 was administered without NO, pulmonary vascular resistance did not decrease below the baseline measurements. Use of INO during cardiac catheterization allows the physician to determine which children are unable to reduce pulmonary hypertension because of a restricted pulmonary vascular bed.

Concentration of Nitric Oxide

Varying NO concentrations have been studied to determine which best produces pulmonary vasodilation while minimizing toxic effects. Clark et al[4] gave neonates 10 ppm of NO for a maximum of 24 hours and 5 ppm for no more than 96 hours. ECMO was used on 64% of the control group and 38% of the NO group ($P = 0.001$). The 30-day mortality rate was similar for the control group (8%) and for the NO group (7%). There was less chronic lung disease in the NO group (7%) compared to 20% in the control group ($P = 0.02$).

Davidson et al[6] studied NO 5 ppm, 10 ppm, or 80 ppm. Most patients demonstrated improvement in oxygenation with NO. Only patients with 80 ppm NO demonstrated elevated methemoglobinemia and nitrogen dioxide (NO_2) levels. None of the patients had prolonged bleeding times.

The Franco-Belgium Collaborative NO Trial Group[11] studied preterm and near-term neonates with respiratory failure. The need for mechanical ventilation and length of stay in the intensive care unit was shortened, while oxygenation was improved, on low-dose (10 ppm) NO for near-term neonates. NO did not prove beneficial for preterm neonates.

The Neonatal Inhaled Nitric Oxide Study Group[20] studied INO and respiratory failure in infants with congenital diaphragmatic hernia (CDH). INO was not found to be effective in improving oxygenation of infants with CDH.

Miller et al[18] used very low-dose INO (2 to 20 ppm) to treat pulmonary hypertension following congenital heart repair surgery. Pulmonary vasodilation was effective in patients with high pulmonary vascular resistance, especially if the pulmonary artery pressure/systemic arterial pressure ratio was high. Low-dose NO may decrease the toxic effects of NO.

Curran et al[5] studied postoperative repair of congenital heart patients utilizing INO for postoperative pulmonary hypertension. Five patients had complete atrioventricular canal. These patients were treated with conventional measures—hyperventilation, F_{IO_2} 0.80, and inotropic agents. When INO was added, there was no statistical difference between conventional treatment and NO.

An additional 15 postoperative congenital heart defect patients with a variety of defects were studied.[5] These patients had refractory pulmonary hypertension and were given INO. Eleven patients had good results when INO was given at low concentrations (10 to 20 ppm). Curran[5] stated that if low concentrations (20 ppm or 40 ppm) did not produce pulmonary vasodilation, higher concentrations were ineffective.

Davidson et al[6] also demonstrated that 80 ppm NO showed no advantage over NO at 5 ppm and 20 ppm.

Toxic Effects of Nitric Oxide and Treatments

When NO binds with hemoglobin, it forms methemoglobin, which can effect the ability of oxygen to bind to hemoglobin and thereby decrease oxygenation.[26] Methemoglobin levels should be kept lower than 5%.[19, 20] Lowering the amount of NO administered in 20% decrements,[6] or lowering NO by 50%,[5] decreases the amount of methemoglobin in the blood. If methemoglobin does not correct to a satisfactory level with decreasing NO, NO can be stopped and methylene blue can be given intravenously, 1 to 2 mg/kg[3, 26] over 5 minutes, repeated in 1 hour if needed. (If methylene blue is used, urine and feces will have a blue-green color.[3]) Wessel et al[29] decreased methemoglobin by giving 500 mg vitamin C injections and a blood transfusion.

Methemoglobin is metabolized by methemoglobin reductase.[29] Members of some ethnic groups and low-birth weight neonates may have a deficiency of methemoglobin reductase. INO byproducts are removed within 48 hours by urine, feces, and salivary glands.

NO is oxidized to form nitric dioxide, which can damage the lungs,[5, 10, 17, 24] and may cause pneumonitis, pulmonary edema, emphysema, or death. Studies have shown that formation of nitric dioxide can be minimized when NO has a short interaction with oxygen, which can be accomplished by delivering NO proximally or distally to the inspiratory limb.[17] Besides a short interaction time between oxygen and NO, levels of NO and oxygen should be kept at the lowest effective levels.[10] Levels of NO and nitric dioxide must be monitored at, or distal to, the patient to detect toxic levels.[17] NO should be decreased if nitric dioxide exceeds 7 ppm.[20] Nonventilator patients can receive NO by using a non-rebreather mask,[17] with NO delivered through a one-way valve.[29] The above recommendations of short interaction of oxygen and NO and monitoring of the NO/NO_2 should also be followed with NO by mask.

Nitric oxide also is associated with affecting platelet function, which could increase bleeding. The exact mechanism has not been determined.[19]

Weaning Nitric Oxide

Davidson et al[7] investigated successful weaning from INO. After treatment was determined to be a success or failure, the treatment gas was decreased by 20% in five steps. Oxygenation was monitored and remained stable during the initial weaning of 0, 5, 20, and 80 ppm of treatment gas. However, when the treatment gas was stopped, three NO groups showed a decrease in oxygenation. The decrease was statistically significant as well as clinically noted in the 4 ppm and 16 ppm groups but not the 1 ppm group. There were no adverse effects from the withdrawal of the INO. Careful monitoring and weaning is necessary to prevent rebound pulmonary hypertension.

This study suggested that F_{IO_2} should be increased by 20% with the cessation of the INO to prevent decreased oxygenation.[7] Infants who are treatment failures should be kept on INO while being placed on ECMO or transferred to an ECMO center. Stopping INO may cause rapid deterioration and life-threatening hypoxemia.

SUMMARY

NO has been used successfully to treat PPHN, reducing the need for ECMO. NO has also been used in the cardiac catheterization laboratory to determine if pulmonary hypertension will decrease with NO. Patients who do not respond to NO are at higher risk after open-heart surgery, because their pulmonary hypertension will be difficult to treat. Postoperatively, NO can be used to determine if pulmonary hypertension is caused by vasoconstriction or by an obstruction.

Inhaled Nitric Oxide at a Glance

- Action: Selective pulmonary vasodilation without systemic vasodilation.
- Use: Treatment of pulmonary hypertension.
- Concentration and route: Lowest concentration that will produce pulmonary vasodilation and improved oxygenation.
  Concentration should be kept < 80 ppm.
- Contraindication: Neonate that is ductal-dependent.
- Toxic effects: Keep methemoglobin level < 5%.
  Keep nitric dioxide, which can cause lung damage, < 7 ppm.
  Risk of bleeding.

- Monitor: Levels of NO/NO_2.
  Platelets.
  Arterial blood gas (ABG).
  Methemoglobin.
- Weaning: Decrease NO by 20%, monitoring ABG at 3- to 4-hour intervals.
  If there is a decrease in oxygenation, increase NO.
  Increase F_{IO_2} 20% when NO is discontinued.
  Unsuccessful treatment with NO—keep on NO until ECMO is available.

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