Pilbeam: Mechanical Ventilation, 4th Edition

Special Techniques in Mechanical Ventilation

SECTION IV: Nitric Oxide

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LEARNING OBJECTIVES

Upon completion of this section the reader will be able to do the following:

1. Describe physical characteristics of nitric oxide.
2. List the normal concentration range for ambient nitric oxide, inhaled nitric oxide levels in smokers, and therapeutic levels of inhaled nitric oxide.
3. Explain the cellular process in which endogenous nitric oxide is produced.
4. Discuss the effects of inhaled nitric oxide on the pulmonary circulation, ventilation/perfusion matching, and pulmonary shunt.
5. Identify side effects and complications of inhaled nitric oxide.
6. Name the medication used in treating methemoglobinemia.
7. Compare the use of inhaled nitric oxide in patients with persistent pulmonary hypertension of the newborn and those with acute respiratory distress syndrome.
8. Describe the advantages and disadvantages of the four nitric oxide delivery systems presented.

In certain pulmonary disorders such as persistent pulmonary hypertension of the newborn (PPHN) and acute respiratory distress syndrome (ARDS), pulmonary vasoconstriction and pulmonary hypertension contribute to shunting and hypoxemia. In an effort to find a way to reverse these difficulties, a simple, common gas molecule called nitric oxide (NO) has been studied and used as a potential treatment to improve oxygenation and reduce shunting. This section reviews the use of NO as a therapeutic inhaled gas.

PROPERTIES OF NO

NO is a highly reactive gaseous radical commonly found in the environment. Between 10 and 100 ppb are present in the atmosphere. Smokers may inhale as much as 400 to 1000 ppm when they inhale tobacco smoke.[1] Although NO is normally present in our environment, it is still considered an air pollutant.[2] In fact, NO is even present in the compressor gas supplies of hospitals, and breathing these gases may affect patients.[3]

 NO is endogenous to and produced by a variety of body cells. It is also an important messenger molecule. For example, NO is accountable for the activity of the endothelium-derived relaxing factor, an agent that relaxes smooth muscles and augments blood flow in veins. The effectiveness of certain medications, such as sodium nitroprusside and nitroglycerin, is in fact attributed to their release of NO.

 The formation of NO in cells is dependent on the presence of L-arginine, an amino acid. NO is produced in the presence of NO-synthase, an enzyme. The resulting NO typically diffuses to a neighboring cell where it binds with and activates guanylate cyclase. In the presence of guanosine triphosphate, activated guanylate cyclase increases production of cyclic guanosine 3′,5′-monophosphate, which produces certain biological effects within cells, such as smooth muscle relaxation (Figure 1).[4]
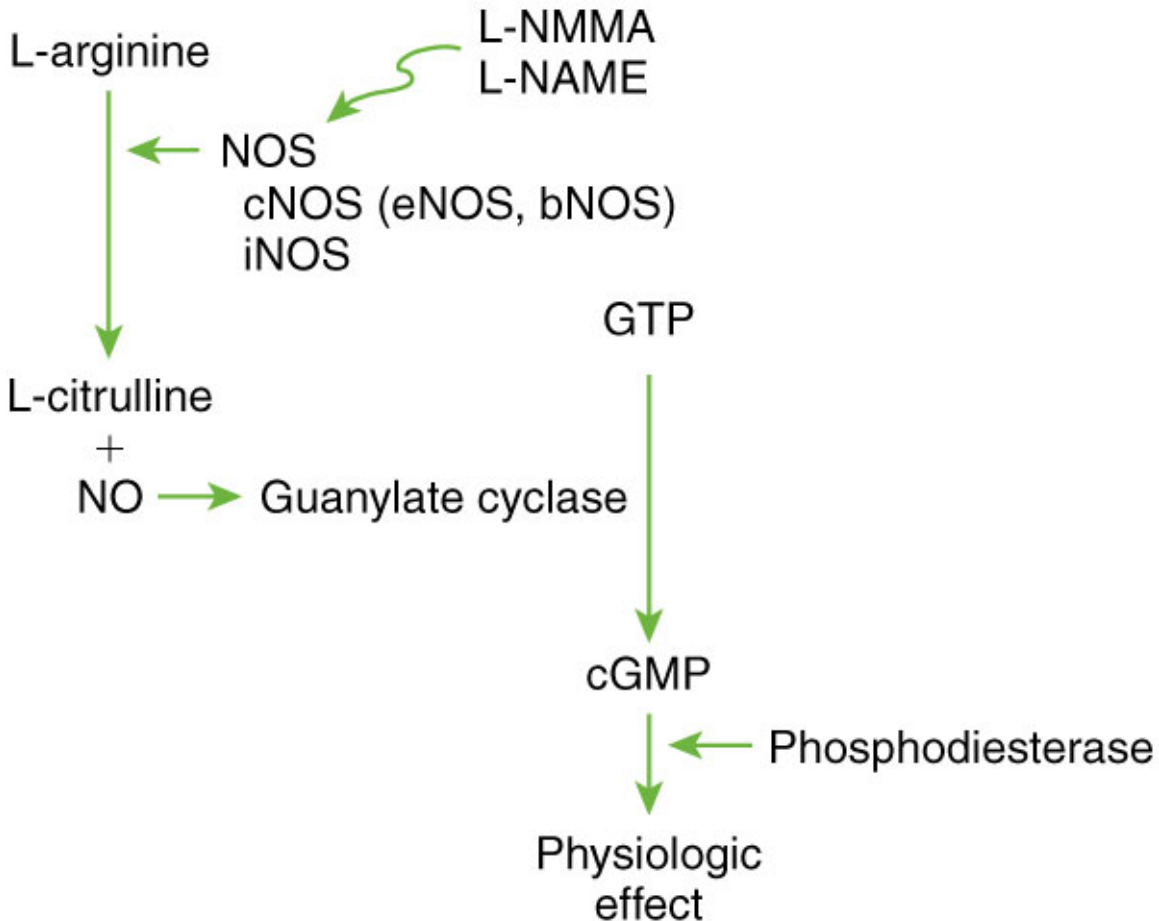
Fig. IV-1

Biological pathway for the endogenous production of NO. *bNOS,* Neuronal-type constitutive NO synthase; *cGMP*, cyclic guanosine 3′5′-monophosphate; *cNOS,* constitutive NO synthase; *eNOS,* endothelial NO synthase; *GTP,* guanosine triphosphate; *iNOS,* inducible NO synthase; *L-NAME, L-NG,* arginine methyl ester; *L-NMMA,* L-NG-monomethyl arginine; *NOS,* NO synthase. (From Hess D: Heliox and inhaled nitric oxide. In MacIntyre NR, Branson RD: *Mechanical ventilation*, Philadelphia, 2001, Saunders.)

NO has been measured in exhaled gases and within the nasopharynx and the paranasal sinuses in human beings.[5,6] The NO in the nasopharynx is actually inhaled and absorbed. NO present in the paranasal sinuses may have a bacteriostatic effect within the sinuses.[6] In inflammatory conditions such as asthma and bronchiectasis, the amount of exhaled NO increases above the normal amount. This may be a result of increasing NO synthesis from neutrophils and macrophages.[7]

SELECTIVE PULMONARY VASODILATION

NO is important to pulmonary medicine because it can be inhaled through the lungs and cause selective pulmonary vasodilation. When very low concentrations of NO (0.25 to 20 ppm by volume) are inhaled in the lungs and delivered to ventilated alveoli, vasodilation

of adjacent pulmonary vessels occurs, resulting in improvement in ventilation/perfusion

($\dot{V}/\dot{Q}$) matching, reduction of shunting, and increase of PaO_2.[8,9] This occurs without dilating systemic vessels because the inhaled NO rapidly combines with hemoglobin once it diffuses into the blood stream and is inactivated. NO is not in itself a selective pulmonary vasodilator, but it becomes one when administered as an inhaled gas.[4] Other intravenous vasodilators such as nitroglycerin and sodium nitroprusside are not selective. These vasoactive agents result in lower systemic and pulmonary blood pressure. In addition, they increase blood flow to both ventilated and nonventilated alveoli, which increases intrapulmonary shunting and reduces arterial oxygenation.[10]

TOXIC EFFECTS AND COMPLICATIONS OF INHALED NO

Inhaled NO, although beneficial as a selective vasodilator, has undesirable side effects. Most of these effects are minimal when NO is administered in appropriate amounts by experienced practitioners. However, clinicians using the gas should be familiar with the potential complications.

Direct Inhalation of High Concentrations

Direct inhalation of extremely high concentrations of the NO gas either by accidental iatrogenic administration or in farmers exposed to the gas when filling silos (silo filler's disease) can result in shortness of breath, hypoxemia, pulmonary edema, and even death.[11,12] Although actual amounts of NO inhaled are not addressed in this section, one can only imagine the quantity of NO sufficient to cause death if cigarette smoke can contain as much as 1000 ppm. Table 1 illustrates some of the responses detected at various concentrations of NO administered to human beings.[4]

Table 1
Response in Human Subjects Exposed to Various Concentrations of Inhaled NO

Exposure Amount of NO	Response
1 ppm	Small decrease in specific airway conductance in healthy volunteers
15-20 ppm	A decrease in PaO_2 and an increase in airway resistance in normal subjects after 15 min
80 ppm	Decreased airway conductance in patients with chronic obstructive pulmonary disease

Nitrogen Dioxide

NO rapidly combines with oxygen to form the toxic irritant nitrogen dioxide (NO_2). Exposure to NO_2 has been shown to result in lung injury, loss of cilia, hypertrophy, and focal epithelial hyperplasia of the terminal bronchioles in rats.[13] In the presence of water, NO_2 forms nitric acid. The precise effects of these substances on human lungs are being investigated.

Methemoglobin

After exposure to high levels of NO gas (80 ppm), the level of methemoglobin (metHb) in the blood increases.[4] (Note: Therapeutic inhalation of 20 ppm NO or less does not typically produce methemoglobinemia.) MetHb is a form of hemoglobin in which the iron molecule in the heme portion has been converted from the normal ferrous state (Fe^{+2}) to the oxidized ferric state (Fe^{+3}). MetHb is commonly present in concentrations less than 2%. This normal amount may actually exist because of the metabolism of endogenous NO.

When NO reacts with oxyhemoglobin it forms inorganic nitrate and methemoglobin. Inorganic nitrate is unstable and reacts with hemoglobin to form methemoglobin and NO. The NO reacts with oxyhemoglobin, and so on.

MetHb blood levels of less than 5% do not require treatment. However, higher percentages of metHb do require treatment because metHb interferes with the oxygen-carrying capacity of the blood. MetHb cannot bind to oxygen, and its presence actually interferes with the ability of normal hemoglobin to carry oxygen (leftward shift of the oxyhemoglobin dissociation curve). Methylene blue infusion is the common treatment for high metHb levels. Methylene blue increases reduced nicotinamide adenine dinucleotide metHb reductase. Ascorbic acid (vitamin C) can also be used for treatment.[4]

Peroxynitrite

Peroxynitrite ($ONOO^-$) is a toxic substance produced when endogenous NO reacts with an oxide radical (O_2^-): $NO + O_2^-$ yields $ONOO^-$. This can occur in biological systems and may have toxic effects on these systems.[14] Whether inhaled NO produces a reaction is not currently known.[4]

Platelet Inhibition

NO may inhibit platelet adhesion, aggregation, and agglutination. The importance of this clinical side effect has yet to be determined.[15]

NO in Patients with Severe Left Ventricular Dysfunction

In some patients with severe left heart failure, high levels of inhaled nitric oxide (40 to 80 ppm) have been shown to reduce pulmonary vascular resistance and increase pulmonary artery occlusion pressure.[16] With a drop in pulmonary vascular resistance and therefore a decrease in afterload to the right heart, improvement in right heart output increases venous return to the left ventricle. If the left ventricle is functioning poorly, the resulting increased left ventricular filling may worsen pulmonary edema. This response may be dose related. In patients with elevated pulmonary artery occlusion pressure (25 mm Hg or greater) and severe left ventricular dysfunction, inhaled NO therapy should be avoided.[4]

CLINICAL APPLICATION

Because of its properties, inhaled NO is being used to manage patients with PPHN, ARDS, and congenital heart disease.[17,18] The response to NO inhalation varies between the type of pulmonary problem and individuals. Some patients have significant decreases in pulmonary vascular resistance and improvements in oxygenation, and others do not respond at all.[19]

PPHN

Box 1 describes the condition known as PPHN.[20] Treatment of PPHN is generally directed at the known cause—for example, oxygen therapy for hypoxemia, surfactant for respiratory distress syndrome, glucose for hypoglycemia, and inotropic agents for low cardiac output and systemic hypotension.[20] If hypoxemia persists in spite of therapy, intubation and mechanical ventilation are typically required. Alternative treatments include high-frequency ventilation and inhaled NO. (See Chapter 22 for information on high-frequency ventilation.) Rescue therapy might include high-frequency ventilation or exogenous surfactant along with NO. When all of these treatments fail, extracorporeal life support (also known as extracorporeal membrane oxygenation [ECMO]) may be instituted. (See section on extracorporeal gas exchange techniques on this Web site.)

Box 1 PPHN

Under normal conditions after birth, as the lungs become aerated, pulmonary vascular resistance decreases as the pulmonary veins become well oxygenated. At the same time, systemic vascular resistance increases as the placenta is removed from circulation. PPHN is a complex syndrome that presents after birth when the normal transformation of fetal circulation to extrauterine circulation does not take place.

Three functional types of PPHN exist:
1. Vascular spasm triggered by many different conditions (e.g., hypoxemia, hypoglycemia, hypotension, pain)
2. Increased muscle wall thickness, a chronic condition that develops in utero in response to several factors (e.g., chronic fetal hypoxia, increased pulmonary blood flow, pulmonary venous obstruction)
3. Decreased cross-sectional area of pulmonary vessels

PPHN is suspected if the infant has rapidly changing oxygen saturations without any change in F_IO_2. It is also suspected if hypoxemia is out of proportion to the pulmonary disease identified with chest radiography or $PaCO_2$ values. In infants with suspected PPHN who have a significant right-to-left shunt through the ductus arteriosus, a large difference between SpO_2 values measured on the right arm and on a leg is usually present.

In patients with moderate PPHN, treatment with NO improves oxygenation (PaO_2) and reduces the amount of ventilatory support required. Thus inhaled NO used in moderate PPHN may prevent progression to severe PPHN.[21] The use of NO therapy may reduce the requirement for ECMO in infants with severe PPHN (e.g., P[A-a]O_2 greater

than 600 mm Hg).[21,22] However, NO may not be beneficial in patients with a high degree of structural pulmonary abnormalities (hypoplasia or alveolar capillary dysplasia) that interfere with the action of the gas. In patients with PPHN and congenital diaphragmatic hernia, NO remains an unproven treatment and ECMO should not be postponed in those fulfilling ECMO criteria.[23]

NO Use in Other Neonatal Disorders

In addition to PPHN, a number of other clinical conditions can result in hypoxemic respiratory failure in the newborn, including meconium aspiration, pneumonia, and respiratory distress syndrome. When inhaled NO is used in conjunction with conventional treatment strategies, such as mechanical ventilation, surfactant therapy, and high-frequency ventilation, infants treated with NO have a lower mortality rate and less need for extracorporeal life support.[24]

ARDS

ARDS is an inflammatory process in the lungs that results in pulmonary edema, severe hypoxemia (PaO_2/F_IO_2 less than 200), reduced lung compliance, and increased shunt. (See Chapter 14 for additional information on ARDS and its management.)

The use of NO in patients with ARDS was first reported by Rossaint et al,[9] who reported a reduction in pulmonary artery pressures, an increase in PaO_2, and a decrease in shunt. Similar findings were reported by others.[18] In patients with ARDS, the most appropriate dose of NO appears to be low (5 ppm).[4]

Meade and Herridge[8] evaluated the results of four large studies using inhaled NO in patients with acute lung injury and ARDS. Their results concluded that none of the studies found an important survival benefit, and that although inhaled NO therapy could produce dramatic improvements in oxygenation in some patients, no evidence that it improved outcome was found. They recommended that NO therapy be limited to salvage therapy in patients in respiratory extremis only.

Lung Transplantation

In a study of 14 patients receiving lung transplantation for end-stage lung disease and pulmonary hypertension, NO demonstrated no harmful side effects, did not lengthen the time on mechanical ventilation, and may have reduced the incidence of acute graft rejection.[25]

SYSTEMS FOR DELIVERING INHALED NO

When the decision is made to used NO for therapy, the procedure for its administration must include a few key factors (Box 2).[4] The four basic types of systems for NO delivery are a commercially available system (I-NOvent Delivery System, Datex Ohmeda, Madison, Wis.), one used with a continuous-flow ventilator such as those used with pediatric ventilation, a premixed NO system, and an NO injection system.

Box 2   Important Considerations when Designing an In-house System for
Delivering NO to Ventilated Patients

The delivery system must be simple to operate and dependable.

The dose of NO should be stable and precise.

Levels of NO and NO_2 need to be monitored.

The level of NO_2 inhaled must be kept as low as possible.

The delivery system should not interfere with ventilator function.

F_IO_2 is monitored after the connection where NO is titrated into the system because NO decreases F_IO_2.

I-NOvent Delivery System

The I-NOvent Delivery System is designed to be used with any type of ventilator, including a high-frequency oscillator (Figure 2).[26] The system is typically mounted on a transport cart with two NO gas cylinders. An injection module from the unit is positioned on the inspiratory side of the patient ventilator circuit near the port where the gas flow comes from the ventilator and goes to the patient. The injection module contains a flow sensor and gas injection tube. The flow sensor precisely monitors the flow coming from the ventilator. NO is injected in proportion to the flow measured and the set NO dose selected (range, 0 to 80 ppm by an 800-ppm cylinder). The device uses either a high- or a low-flow controller, which ensures that the I-NOvent is able to deliver an accurate concentration of desired NO over a wide range of flows (neonatal to adult patients). The sensors measure O_2, NO, and NO_2 from gases sampled near the ventilator Y-connector. The top-mounted display console (see Figure 2) provides a digital readout of parameters. Available alarms are listed in Box 3.

Fig. IV-2
The I-NOvent Delivery System. (Courtesy Pamela West, RRT, Medical Center of Central Georgia, Macon, Ga.)

Box 3 Available Alarms on the I-NOvent Delivery System
High and low NO
High NO_2
High and low O_2
Calibration required
Electrochemical (gas monitoring) sensor failure or weakening
Monitoring failure
Loss of gas pressure
Delivery system failure

Continuous-Flow Ventilator System

In pediatric ventilators that use continuous flow for patient ventilation, a system has been described for titrating NO into the inspiratory line of the ventilator.[27] The schematic drawing of a NO delivery system shown in Figure 3 has been used in continuous-flow pediatric ventilators.
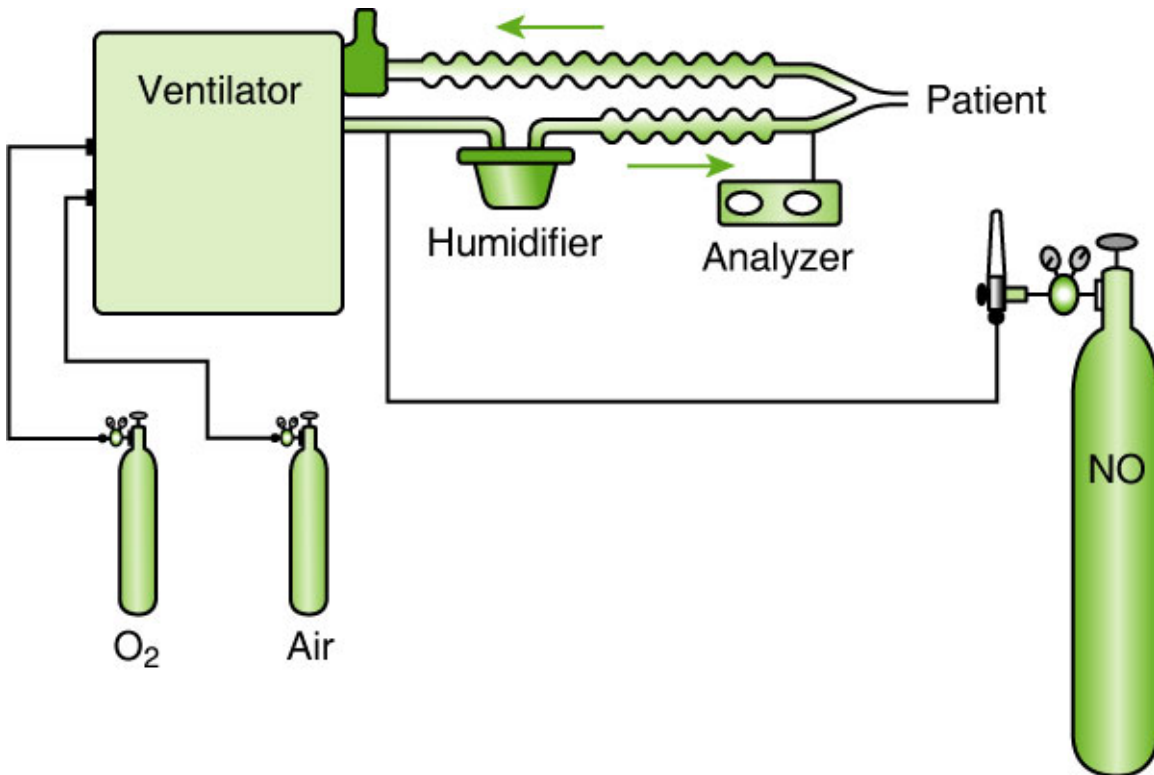
Fig. IV-3
Schematic drawing of a delivery system for inhaled NO using a continuous-flow pediatric ventilator. (From Hess D: Heliox and inhaled nitric oxide. In MacIntyre NR, Branson RD: *Mechanical ventilation*, Philadelphia, 2001, Saunders.)

The design works as follows. NO from a cylinder source is infused into the inspiratory limb of the ventilator near the ventilator. The analyzer is mounted at least 30 cm (12 inches) from this connection to ensure adequate gas mixing and avoid dosing errors.[4] Because the residual time of NO in the system is short, the generation of NO_2 should be low. The expected NO dose is calculated as follows[4]:

NO dose = (NO flow × Source [NO] concentration)/(NO flow + Ventilator flow)

High-frequency oscillation (HFO) is another technique used in the management of severe hypoxemia in infants. HFO incorporates a continuous bias flow of gas. Studies have shown that NO can be injected in several sites into the circuit at a continuous titration rate and that NO mixing is adequate. Injection upstream from the humidifier (prehumidifier) during HFO is preferable because it produces the smallest amount of

fluctuation in NO gas concentration.[26] (For information on HFO, see Chapters 22 and 23.)

Premixed NO System

Figure 4 illustrates a system of premixing of NO before delivery of the gas into a ventilator circuit. A gas blender is used to accurately control mixing of a controlled amount of NO (e.g., 800 ppm), which is connected to the O_2 inlet of the blender while either nitrogen (N_2) or air is connected to the air inlet of the blender. These mixed gases are added to the gas inlet of the ventilator. N_2 should be used instead of air with high doses of NO (more than 20 ppm), high F_1O_2 delivery (more than 0.9), or low minute volume settings.[28] NO dose and F_1O_2 delivery should be confirmed by gas analysis (see Figure 4).
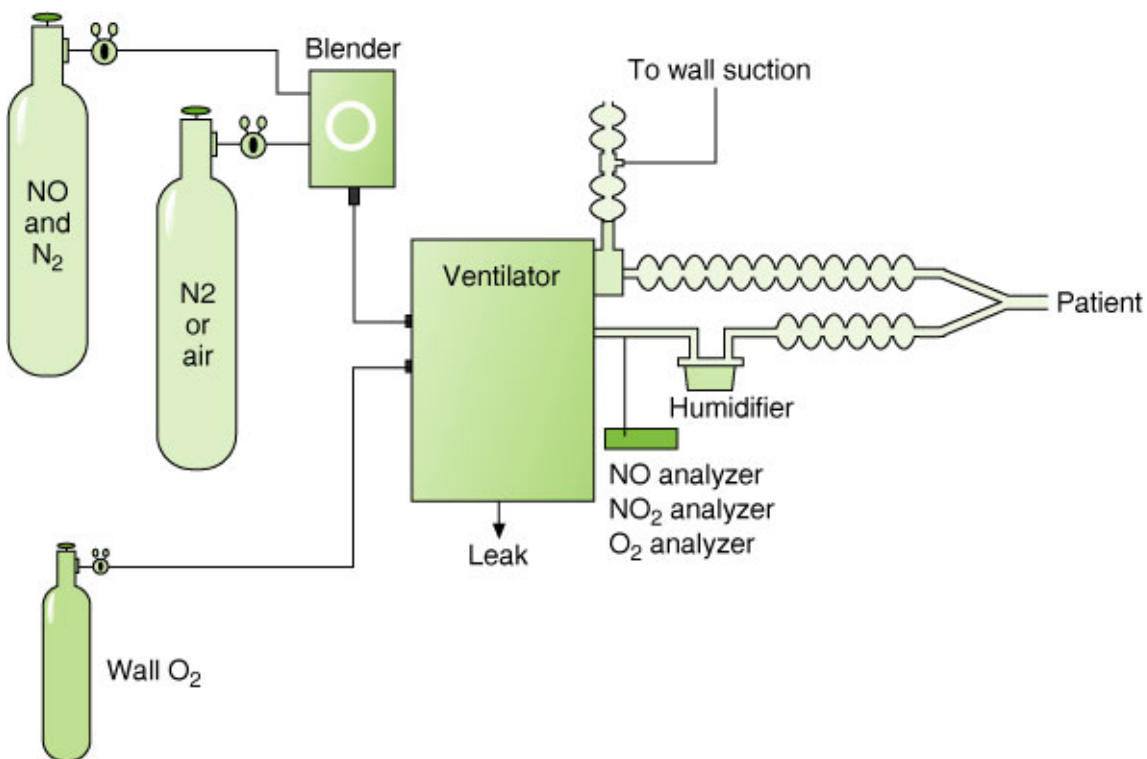
Fig. IV-4
Schematic drawing of a premixing NO delivery system. NO (800 ppm) is mixed with N_2 or air and introduced into the air inlet of a ventilator. The settings on the external blender and ventilator F_1O_2 control determine the delivered NO concentration. (From Hess D, Bigatello L, Kacmarek RM, et al: *Respir Care* 41:437, 1996.)

NO Injection System

NO injection systems use a continuous flow of NO added to the inspiratory limb of a ventilator to administer NO. The mean NO dose delivered to the patient is estimated by the following equation[4]:

$$NO\ desired = NO\ flow \times source\ (NO)/\dot{V}_E$$

This type of NO delivery is not recommended for conventional ventilation for several reasons. First, the inspiratory circuit fills with NO during expiration when the patient circuit is sealed. Thus, during the next mandatory breath delivery, a high dose of NO is administered with the breath.[29] This produces large fluctuations of NO that go undetected if a rapid-response NO analyzer is not used.[30] If mandatory breaths are mixed with spontaneous breaths, as with synchronized intermittent mechanical ventilation, NO delivery is even more inconsistent from breath to breath. Second, the added flow into the circuit may make it difficult for the ventilator to sense a patient's inspiratory breath and may fail to trigger a breath. Third, the patient may receive an oxygen-deficient breath. During low tidal volume delivery, the volume of NO in any single breath may represent a sufficient part of the breath, thus reducing the available oxygen to the patient.[4] Fourth, the concentration of NO delivery by this method is affected by flow waveform selected, changes in flow, $\dot{V}_E$ setting, and the site where the NO is injected.

Scavenging NO from Delivery Systems

The Occupational Safety and Health Administration sets limits on the exposure time of health care providers to NO and NO_2 (time-weighed average of 25 ppm over an 8-hour period).[4] This is higher than the typical amount of NO present during inhaled NO dose (20 ppm or less). The amount of ambient NO present when inhaled NO is being used therapeutically has been measured in very low amounts (less than 0.25 ppm) whether efforts were made to scavenge the NO from the system or not.[4,31] Even using scavenger systems to uptake a ventilator's vented gases is not completely efficient because ventilator circuits typically have small leaks. With a scavenger system in use, the system should not impede the outflow of exhaled gas or alter ventilator function. One possible option for cleaning vented gases is to allow a ventilator's exhaled gas to pass through a canister of potassium permanganate and charcoal to remove NO and NO_2.[4]

WITHDRAWAL OF INHALED NO

During daily attempts at withdrawal of inhaled NO in some patients, rebound hypoxemia and pulmonary hypertension may occur.[9,32] The reason for this rebound effect is not known. To help avoid this potential problem associated with NO withdrawal, the following steps are recommended[4]:

1. Use the lowest effective dose of NO during therapy (5 ppm or less).
2. Maintain NO therapy until the patient's clinical status is improved (i.e., positive end-expiratory pressure of 5 cm H_2O, F_IO_2 0.4 or less).

3. Prepare to maintain the hemodynamic status of the patient if necessary.
4. Increase the F_IO_2 to 0.6 to 0.7 before withdrawing the inhaled NO.

Inhaled NO may be cost effective and appropriate for rescue therapy of selected infants with PPHN.[33] Although NO may transiently improve oxygenation in adults and children with acute hypoxic respiratory failure, lack of sufficient data prevents determination of the effectiveness of inhaled NO in reducing mortality rate.[8,34] The use of alternative treatments, such as HFO and surfactant, may be as effective with or without the administration of NO. A recent alternative to inhaled NO in adult patients may be nebulized Flolan, which may be as effective and less costly than inhaled NO. This alternative medication warrants study.

REVIEW QUESTIONS

1. Which of the following is true regarding the characteristics of NO?
    I.   NO occurs endogenously in cells
    II.   NO is normally present in ambient air
    III.   Normal ambient concentration of NO is 400 ppm
    IV.   NO is formed in cells by using L-arginine
  a. I only
  b. III only
  c. II and IV
  d. I, II, and IV
2. Which of the following are benefits of using NO inhalation in some patients?
    I.   Reduces systemic blood pressure
    II.   Produces selective vasodilatation of pulmonary vessels
    III.   Increases diffusion of O_2 across the alveolar-capillary membrane

    IV.   Improves $\dot{V}/\dot{Q}$ matching
  a. III only
  b. II and IV
  c. I and III
  d. I, II, and IV
3. Toxic effects of and complications from inhaled NO include which of the following?
    I.   Direct inhalation of high concentrations results in shortness of breath, hypoxemia, pulmonary edema, and even death.
    II.   Combining NO and O_2 produces NO_2, a toxic irritant.
    III.   MetHb can be produced when high levels of NO are inhaled.
    IV.   NO may inhibit platelet adhesion.
  a. II only
  b. III only
  c. I and IV
  d. I, II, III, and IV
4. Inhaled NO has been used clinically in all *except* in which of the following disorders?
  a. Severe left ventricular failure
  b. PPHN

    c. ARDS
    d. Lung transplant

5. Which of the following delivery systems may result in uneven delivery of inhaled NO and difficulty for the patient in triggering the ventilator?
    a. Commercially available system (I-NOvent Delivery System)
    b. NO injection system
    c. Continuous-flow pediatric ventilator
    d. Premixed NO system

ANSWERS TO REVIEW QUESTIONS

1. d
2. b
3. d
4. a
5. b

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