Inhaled nitric oxide (NO) is a selective pulmonary vasodilator in adult and pediatric patients. Inhaled NO diffuses into the pulmonary vascular smooth muscle where it results in vasodilation via stimulation of guanylyl cyclase. Systemic hemodynamics are not altered because inhaled NO is rapidly inactivated by hemoglobin. Oxygenation is also increased in certain patients as inhaled NO only vasodilates those segments of the pulmonary vasculature which are ventilated. There is growing evidence that inhaled NO may be a useful therapeutic agent in the treatment of pulmonary hypertension and hypoxemia from a variety of causes.

Areas of greatest interest to anesthesia and critical care personnel may involve treatment of persistent pulmonary hypertension of the newborn (PPHN), adult respiratory distress syndrome (ARDS), and postoperative pulmonary hypertension secondary to cardiac disease. The potential toxicity of inhaled NO, particularly on immature and developing lungs, must be considered. While inhaled NO exerts acute beneficial effects, it is unclear if there are long-term benefits. Multicenter trials are currently underway to determine if inhaled NO decreases mortality from PPHN or decreases morbidity associated with ARDS.

Key words: Endothelium-derived relaxant factor, nitric oxide, nitric oxide synthase, pulmonary hypertension, pulmonary vasodilation.

Endogenous nitric oxide
The vascular endothelium plays an important role in modulating vascular smooth muscle tone. The endothelium contains vasoactive substances which are basally released and also respond to various agonists. These vasoactive agents act on the underlying vascular smooth muscle and cause either relaxation or constriction.

In 1980, an unidentified vasodilating factor released from endothelium was reported as the mediator of acetylcholine-induced vasodilation and named endothelium-derived relaxant factor (EDRF).1 EDRF diffuses from the endothelium into the vascular smooth muscle where it activates soluble guanylyl cyclase to produce an increase in cyclic 3',5' guanosine monophosphate (GMP) and results in vascular relaxation. In 1986, EDRF was recognized as nitric oxide (NO).2,3

NO is now known to be a novel signaling molecule with wide ranging physiologic and pathophysiologic actions in the cardiovascular, immune, and nervous systems. NO plays a major role in disease states such as atherosclerosis and hypertension, cerebral and coronary vasospasm, and ischemia-reperfusion injury. In the immune system, it is an effector mechanism for macrophage induced cytotoxicity,4 and its overproduction is an...
important mediator of the septic shock syndrome. In neuronal tissue, NO appears to subserve multiple functions. Recent studies have suggested a role for NO in mediating central nociceptive pathways and a possible involvement in mechanisms of anesthesia.

NO has a significant role in maintaining the normal low resting pulmonary vascular tone. Flow or shear stress-induced vasodilation in the pulmonary circulation may also be mediated by NO release. In blood vessels, NO is produced by endothelium where it is a primary determinant of resting vascular tone through basal release and causes vasodilation when synthesized in response to a wide range of vasodilator agents. The common nitrovasodilators, nitroglycerin, and sodium nitroprusside release NO from within their molecules and cause vasodilation of both the pulmonary and systemic circulations. Bradykinin and acetylcholine stimulate the release of endogenous NO from the pulmonary endothelium and are endothelium-dependent vasodilators. When the endothelium is absent or damaged, these agents produce vasoconstriction. Endothelium-dependent vasodilation of the pulmonary vasculature has been shown to be markedly inhibited or abolished in patients with chronic hypoxic cor pulmonale resulting from end-stage chronic obstructive lung disease. In such pulmonary disease states where endothelial and NO function is impaired, several endogenous agents which are normally vasodilators may cause vasoconstriction and contribute to increased pulmonary vascular resistance (PVR).

NO is synthesized from L-arginine by the enzyme nitric oxide synthase (NOS). Three major NOS isoforms have been described. They are biochemically similar while retaining important differences. Two require calcium and calmodulin binding for activation and are constitutively expressed (i.e., normally present) in neurons (nNOS) and in endothelium (eNOS). The two constitutive enzymes are activated by a rise in cytosolic free Ca$^{2+}$ and subsequent binding of Ca$^{2+}$ to calmodulin. The third isoform is only expressed following induction by cytokines or microbial products such as endotoxin and participates in host defense, mediating many of the cytotoxic actions of macrophages. This inducible isoform (iNOS) has calmodulin tightly bound as a subunit and produces NO continuously and in large amounts without a calcium requirement. Unlike the constitutive forms, the induced form is present in vascular tissues only following induction by cytokines (e.g., endotoxin induced sepsis). Both inducible and constitutive NO synthases contain a heme moiety and are members of the cytochrome P450 family. These NOS synthases oxidize L-arginine in a stepwise manner to form NO and citrulline as primary products. One molecule of O$_2$ is incorporated into NO and one into L-citrulline.

NO can be inactivated following its production. It binds avidly to hemoglobin and other hemo proteins, and also interacts with superoxide to form peroxynitrite. The regulation of cellular superoxide dismutase activity and subsequent superoxide levels has been suggested as a potential physiological regulatory mechanism. Following its production, the primary biological function of NO is the activation of soluble guanylyl cyclase to increase the cyclic GMP content of several tissues. NO binds with the heme moiety of guanylyl cyclase causing a conformational change and leading to increased catalytic activity. Cyclic GMP then serves as a “second messenger” carrying out many of the actions of NO. (See Figure 1.)

**Inhaled nitric oxide/exogenous nitric oxide**

The use of inhaled NO as a vasodilator developed from an understanding of the actions of en-

![Figure 1](image-url)

**Figure 1**

The endogenous nitric oxide (NO) pathway

- **Agonist**
- **Receptor**
- **Endothelial cell wall**
- **L-arginine**
- **NO synthase**
- **Citrulline**
- **NO**
- **Guanylyl cyclase**
- **GTP**
- **Cyclic GMP**

Endogenous NO is produced in the vascular endothelium and causes vasodilation of underlying vascular smooth muscle by increasing cyclic guanosine monophosphate (GMP). The enzyme NO synthase catalyses the conversion of L-arginine to NO and citrulline. After its production, NO binds to and activates the enzyme guanylyl cyclase which catalyses the production of cyclic GMP from guanosine triphosphate (GTP).
dogenous NO. There has been a dramatic rise in interest in this molecule since it was discovered that inhaled NO decreases PVR without affecting systemic vascular resistance (SVR). Inhaled NO theoretically causes pulmonary vasodilation by the same mechanisms as endogenous NO. Inhalation of NO does not dilate the systemic circulation because it binds rapidly to hemoglobin with a high affinity and is thus inactivated as it is exposed to the pulmonary circulation. Because it is delivered through the respiratory system, inhaled NO is distributed only to those areas of the lung that are ventilated and dilates only those vessels directly adjacent to the ventilated alveolar units. Areas of the lung with collapsed alveoli do not receive NO and remain vasoconstricted. V/Q matching is thus preserved or improved by inhaled NO therapy. In addition to reducing PVR, inhaled NO may improve oxygenation by two mechanisms: (1) by improving V/Q matching, and (2) by increasing pulmonary blood flow. (See Figures 2 and 3.)

Physicians and nurses in anesthesiology may be particularly interested in administering inhaled NO in several situations:

1. Adults with primary pulmonary hypertension.
2. Infants with persistent pulmonary hypertension of the newborn.
3. Newborns with respiratory distress syndrome.
4. Patients with adult respiratory distress syndrome (ARDS).
5. Patients with pulmonary hypertension associated with heart and/or lung surgery.

In addition, inhaled NO may have an investigational diagnostic role in the preoperative assessment of patients being considered for heart and/or lung transplants (see below).

**Treatment for pulmonary hypertension.** Chronic pulmonary hypertension (PHTN) may be associated with pulmonary vascular endothelial dysfunction, and these patients may have reduced endogenous NO synthesis. Inhaled NO may serve as replacement therapy. In 1991, Pepke-Zaba demonstrated that when 40 ppm of inhaled NO was given to patients with severe PHTN, the PVR decreased by 5-68%, but was not associated with a decrease in SVR.27 Several other studies have also demonstrated that when inhaled NO is given to patients with severe PHTN, there is an abrupt decrease in PVR which is not associated with a decrease in arterial pressure or SVR.27-29

PHTN frequently accompanies chronic obstructive lung disease, and in such patients, inhaled NO causes selective pulmonary vasodilation and also improves arterial oxygenation.30 The effects of sustained inhalational NO therapy are also being investigated. A 40-year-old woman with end-stage primary PHTN was successfully managed with inhaled NO at 40 ppm for 68 days until a heart lung transplant was performed.31 In another instance, a 5-month-old child was given 20 ppm inhaled NO for 20 hours followed by 6 ppm for an additional 45 hours resulting in sustained pulmonary vasodilation.32 These reports indicate a role for inhaled NO in the treatment and control of PHTN in cases that are potentially reversible. However, it is unlikely to be beneficial when there is no underlying reversible pathology.

**Treatment for persistent pulmonary hypertension of the newborn.** Endogenous NO production modulates vascular tone in the fetal and postnatal lung and contributes to the normal decline in PVR at birth. It has been hypothesized that decreased release of endogenous NO and other abnormalities in endothelial function may play a critical role in the development of persistent pulmonary hypertension of the newborn (PPHN). PPHN is a life-threatening condition which is characterized by increased PVR, elevated pulmonary arterial pres-
sure (PAP), and right to left extrapulmonary shunting through the patent ductus arteriosus and across the foramen ovale. This results in profound systemic arterial hypoxemia and acidosis. PPHN can result from a variety of neonatal insults such as sepsis (group B streptococcus) and meconium inhalation or may be idiopathic. The histopathological findings include smooth muscle hyperplasia and hypertrophy of the pulmonary arteries. PPHN has a good prognosis if the infant is supported through the acute phase of the illness. Current treatment of PPHN consists of hyperventilation, alkalosis, hyperoxia, inotropic support, and intravenous vasodilators which may themselves add to the morbidity and mortality. Extracorporeal membrane oxygenation (ECMO) is often required but is invasive, expensive, and may predispose to intraventricular hemorrhages.

Inhaled NO has been used to treat PPHN with considerable success improving oxygenation and in some instances obviating the need for ECMO. Finer studied 23 critically ill, hypoxic near-term infants referred for ECMO. Thirteen of these had echocardiographic evidence of PPHN. Eleven of the infants with PPHN responded to inhaled NO (5 to 80 ppm for 15 minutes) with an increase in oxygen index, whereas only 3 of the 10 without PPHN responded. Infants who had a successful response continued to receive the lowest dose of NO associated with improvement (maximum dose = 20 ppm). An attempt was made to wean the infants from NO every 24 hours by decreasing the NO by 5 ppm every 15 minutes. The mean duration of therapy was 40 hours (± 36 hours). Overall, 11 infants required ECMO, 7 of whom had initially responded to inhaled NO. In some infants, improved oxygenation was sustained when inhaled NO was withdrawn after only a few hours. In all these studies, inhaled NO did not cause systemic hypotension. While inhaled NO offers a new approach to the treatment of PPHN, there remain concerns about its potential toxicity on immature lungs. Current ongoing multicenter trials will hopefully enhance our understanding of the effects of inhaled NO in PPHN.

* Treatment for newborns with severe hypoxemia. Neonates with respiratory distress syndrome may develop hypoxemia as a result of right to left extrapulmonary shunt (EPS) or intrapulmonary shunt. EPS through the ductus arteriosus and/or the foramen ovale is the result of increased PVR. Inhaled NO reduces intrapulmonary shunt by improving ventilation-perfusion matching and reduces EPS by decreasing PVR and increasing pulmonary blood flow. Nine infants with hypoplastic lungs requiring ECMO support were given 80 ppm of inhaled NO for 20 minutes before and after treatment with ECMO. Only after decannulation...
from ECMO did NO inhalation increase postductal PaO₂ and arterial oxygen saturation. This could be due to maturational changes occurring in the endothelium while on ECMO.

- Bronchodilation. NO molecules are lipophilic and diffuse through the bronchial epithelial barrier to reach airway smooth muscle cells and produce relaxation. The mechanism of action is likely to be identical to that which produces pulmonary vascular smooth muscle vasodilation. However, the bronchodilator response to inhaled NO is much less and of shorter duration than that regularly observed in asthmatic patients after the inhalation of beta-sympathomimetic drugs. 58, 59

- Adult respiratory distress syndrome. Acute pulmonary hypertension and right to left intrapulmonary shunting of venous blood is common in severe ARDS. Supportive treatment has included intermittent positive pressure ventilation with elevated inspired oxygen concentrations. High levels of inspired oxygen may damage the diseased lung and conventional ventilation has been associated with morbidity secondary to barotrauma and volutrauma. More recently, permissive hypercapnea, placing patients in the prone position, dehydration, and high frequency oscillatory ventilation have been utilized. Severe hypoxemia may also be treated with ECMO or intravenous oxygenation systems. Intravenous vasodilators inhibit hypoxic pulmonary vasoconstriction and decrease PVR in all areas of the lung. The net effect is a decrease in oxygenation secondary to increased venous admixture and/or pulmonary shunt. In marked contrast, inhaled NO decreases PVR and steals blood flow toward ventilated areas (away from collapsed or fluid filled areas of the lung). Therefore, inhaled NO increases arterial oxygenation by reducing intrapulmonary shunting and improving the matching of ventilation to perfusion.

Clinical studies confirm the beneficial effect of inhaled NO in most patients with ARDS, 40-43 but the response varies widely among patients and in the same patient at different times. It is possible that preexisting pulmonary disease and concomitant administration of other drugs may contribute to the variability of response. Pulmonary vasodilation and improvements in oxygenation in response to inhaled NO is greatest in the patients with the highest baseline PVR. 41, 42 Tachyphylaxis does not seem to occur and continuous NO at 5-20 ppb consistently lowered the PAP and improved oxygenation in 7 patients for 3 to 53 days. 40 However, sudden discontinuation of inhaled NO can result in severe pulmonary vasoconstriction and marked deterioration in oxygenation.

Low doses of NO can effectively improve gas exchange. Lowson has demonstrated that decreases in PVR and improvements in oxygenation occur at doses as low as 100 ppb. 42 There does not appear to be additional benefits to delivering greater than 10 ppm. (See Figure 4.)

The risks of toxicity related to inhalational NO (see below) are likely to be reduced if the lowest effective concentration is used. The ability of NO to divert pulmonary blood flow to ventilated lung regions and thereby increase PaO₂ is dependent upon an element of pulmonary vasoconstriction being present, and this may help to determine which patients with ARDS will benefit from inhalational NO therapy. Those with the greatest degree of PHTN appear to respond the most to NO inhalation. So far, decreased morbidity or mortality in patients with ARDS has not been proven, but large randomized prospective trials to determine the benefits of inhaled NO are in progress.

- Adult cardiac surgery. Pulmonary hypertension is a common feature of mitral valve dysfunction and other cardiac diseases. Elevation in PVR often results in right ventricular (RV) failure. Intravenous vasodilators reduce PAP, but the accompanying reduction in systemic pressure can de-

**Figure 4**

Effects of nitric oxide (NO) on hemodynamics and oxygenation in patients with adult respiratory distress syndrome

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<thead>
<tr>
<th>Mean PVRI</th>
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Mean PVRI and PaO₂/FiO₂ values for patients with ARDS before and after NO inhalation. Eight patients with adult respiratory distress syndrome were given inhaled NO at 0.1, 1, and 10 ppm. There was a significant reduction in pulmonary vascular resistance index (PVRI, dyne.s.cm⁻².m⁻¹) and an increase in oxygenation index (ratio of arterial oxygen tension and fraction of inspired oxygen) even with inhaled NO concentrations as low as 0.1 ppm.
crease right coronary perfusion pressure, which further exacerbates RV dysfunction. In contrast, selective pulmonary vasodilation with inhaled NO decreases RV afterload while maintaining coronary perfusion pressure.

Studies have been performed on patients having mitral valve replacement and inhaled NO acted to reduce PVR and PAP. Rich studied 20 patients undergoing coronary artery bypass grafting and demonstrated that 20 ppm inhaled NO was a selective pulmonary vasodilator before and after cardiopulmonary bypass (CPB). Pulmonary vasodilation was proportional to the baseline PVR and was not altered by cardiopulmonary bypass or the infusion of nitrovasodilators.

- **Pediatric cardiac surgery.** Increases in PVR are common in patients with congenital heart disease (CHD). Inhaled NO is the first agent that causes selective dilation in the pulmonary vascular bed in infants with CHD and PHTN, and this has encouraged investigators to use NO to treat postoperative PHTN. Case reports have documented the successful treatment of pulmonary hypertension with inhaled NO after ventricular septal defect repair, arterial switch procedures for transposition of the great vessels, Fontan procedures, and surgery to correct total anomalous venous return. In all instance, inhaled NO decreased PVR without affecting systemic circulation and without apparent side effects.

- **Reversibility-diagnostic studies.** The decision to operate on a patient with pulmonary hypertension may depend on the reversibility of the pulmonary vasoconstriction. If the pulmonary vasculature is responsive to vasodilators, the PVR is more likely to normalize postoperatively once the lesion is corrected. Hypoxic breathing has been used to selectively vasodilate the pulmonary vasculature. Intravenous vasodilators (prostacyclin, tolazoline prostaglandin E₁, sodium nitroprusside) may also be useful but are nonselective and dilate the systemic and pulmonary circulations. Inhaled NO exhibits a far greater selective pulmonary vasodilatory effect than hypoxic breathing and offers an effective alternative.

- **Cardiac transplantation.** Severe preoperative PHTN in heart transplant candidates is associated with increased risk of intraoperative and early postoperative death as a result of acute right ventricular failure of the donor heart after orthoptic heart transplantation (OHT). The right ventricle of the donor heart often develops ischemic injury during the harvesting and implantation procedures, which makes it particularly vulnerable to acute dysfunction and failure when confronted with an increase in afterload. Patients with reversible elevated PVR can be considered suitable for OHT, and an effective vasodilator can be used after surgery to prevent right ventricular failure of the donor heart. By reducing the PVR, inhaled NO is able to unload the nonhypertrophied right ventricle of the newly implanted heart.

- **Lung transplantation.** Acute pulmonary hypertension may be present in patients undergoing lung transplantation. Transient graft dysfunction may occur postoperatively and may be complicated by reperfusion syndrome manifested by PHTN, RV failure, and respiratory failure. A decrease in the endogenous production of NO by damaged endothelium, faster inactivation of NO, or an increase in circulating vasoconstrictors may be implicated in graft dysfunction. Inhaled NO has been shown to reduce PAP and PVR and improve intrapulmonary shunt fraction. Selective pulmonary vasodilation with the associated improvement in intrapulmonary shunting and oxygenation suggests that inhaled NO may be beneficial following lung transplantation.

- **Toxicity of inhaled nitric oxide.** The potential for the clinical use of inhaled NO has to be balanced by the potential toxic effects of this therapy. There are concerns about the immediate direct toxic effects of nitrogen oxides and the formation of free radicals and of methemoglobinemia. Longer term considerations include inhibition of platelet aggregation, modification of the inflammatory response, and mutagenicity. It is also possible that inhaled NO is more toxic to acutely injured and diseased lungs than in the normal.

**Toxicity of nitric oxide and nitrogen dioxide**

NO is a common atmospheric pollutant at levels near 10 ppm. It is present in cigarette smoke (400-1,000 ppm) and is formed in nature by lightning and the burning of fossil fuels. It is also present in the exhaust from motor vehicles. Its major atmospheric breakdown is by combination with ozone.

NO is rapidly converted to nitrogen dioxide (NO₂) in the presence of oxygen within the airways. Even very low concentrations of NO₂ are extremely toxic. The extent of this reaction depends on the concentrations of NO and oxygen and the duration of contact between them. NO reacts with transition metal complexes, including those in metalloproteins such as hemoglobin. The reaction of NO with hemoglobin may protect the systemic circulation from NO toxicity, but the local environment of alveolar lining cells and fluid remains at risk of lung injury.

NO₂ is readily solubilized in the moisture of the respiratory epithelium forming nitric and nitrous
acid. In sufficient concentration, these acids cause severe burns throughout the entire respiratory system. This is the mechanism of silo-filler's disease. The presenting symptoms include dyspnea, cough and wheeze, and there may be signs of infiltrates on chest x-ray or pulmonary edema, hypoxemia, and methemoglobinemia. Clutton-Brock reported two cases of poisoning with NO, NO2, and other higher oxides of nitrogen. This resulted from contamination of anesthesia, nitrous oxide cylinders, and caused acute pulmonary injury, methemoglobinemia, asphyxia, and in one case death. During controlled inhaled NO administration, NO2 concentrations are very low and appear to be safe, although further long-term study is necessary.

Free radical formation

During normal cellular aerobic metabolism, 98% of oxygen is fully reduced to water. About 2% of molecular oxygen is metabolized to superoxide or hydrogen peroxide. These partially reduced oxygen species can directly oxidize biomolecules or be converted into even more reactive species such as the hydroxyl radical. Normally, endogenous tissue antioxidant defenses, such as the superoxide dismutases, maintain intracellular concentrations of reactive oxygen species in the nanomolar range or less. In aqueous solutions, NO reacts rapidly with superoxide to form peroxynitrite which is a strong oxidant in its own right and highly toxic.

The reaction of NO with superoxide may be particularly disconcerting because tissue superoxide formation is increased in a number of situations including hypoxia, ischemia-reperfusion, sepsis, and in both acute and chronic inflammatory disease. In many of these conditions, pulmonary cells are both key sources and targets of reactive oxygen species. The clinical consequences of NO delivery and free radical formation are unknown, although there are no clinical studies which have indicated significant toxicity.

Formation of methemoglobin

In the circulation, NO combines rapidly with hemoglobin to form nitrosyl Fe (II) hemoglobin with an affinity 1,500 times greater than carbon monoxide. When oxygen is present, nitrosyl hemoglobin is oxidized to Fe (III) methemoglobin (MetHb). MetHb is thereafter converted to hemoglobin by the enzyme MetHb reductase, present within the erythrocytes. A small amount of MetHb (1%) is formed in the normal physiological state by auto-oxidation. When patients breathe low concentrations of inhaled NO, most reports indicate only mildly increased and clinically insignificant levels of MetHb. However, high levels have been reported in certain cases. An increased risk for the development of methemoglobinemia is associated with inhalation of high concentrations of NO. Infants are at increased risk because fetal hemoglobin is more prone to oxidation to MetHb than adult hemoglobin (twice the rate), and there is reduced activity of MetHb reductase in the newborn. Certain ethnic groups including Native American Indians and Eskimos have a relative deficiency of MetHb reductase which may place them at a higher risk of developing methemoglobinemia. Prevention of methemoglobinemia involves minimizing NO concentration. It is necessary to monitor MetHb levels at least every 4 hours when initiating inhaled NO therapy.

Inhibition of platelet aggregation

Endogenous NO inhibits platelet aggregation and adhesion at the endothelial cell-blood interface by increasing cyclic GMP. Although some studies have shown prolongation of the bleeding time after NO inhalation and a decrease in ex vivo platelet aggregation, there have been no reports thus far of bleeding complications occurring as a result of inhaled NO therapy.

Mutagenicity

The small molecular size and lipophilicity of NO make it readily accessible to cells. The combination of NO and NO2 yields a potent nitrosylating agent which has been shown to yield carcinogenic N-nitrosamines. The presence of NO in cigarette smoke may contribute to the increased incidence of bronchial carcinoma in smokers.

- Suppression of endogenous nitric oxide. Sudden discontinuation of inhaled NO has been reported to result in severe rebound pulmonary vasoconstriction and marked deterioration in oxygenation. Several recent studies have demonstrated that NO itself acts to regulate its own release by feedback inhibition on NOS. A study by Roos indicated that chronic inhaled NO (20 ppm for 3 weeks) decreased endothelium-dependent vasodilation and the smooth muscle response to NO in hypoxic rats. This is not surprising since it is known that NO donors inhibit NOS in cell cultures. Studies which have demonstrated downregulation of endogenous NO by exogenous NO may explain rebound vasoconstriction and desaturation upon discontinuing inhaled NO. It is, therefore, suggested that inhaled NO be weaned slowly, perhaps to 1 ppm before discontinuation.

- Nitric oxide administration/delivery. Delivery systems for inhaled NO should ensure accurate de-
livery of NO and maintain low levels of NO2. NO should ideally be mixed with the carrier gas (usually O2 and/or air) immediately before inhalation to decrease contact time. Foubert calculated the time to reach 5 ppm NO2 from a mixture of 20 ppm NO in 100% oxygen is 12 minutes and in air is more than 1 hour.70

In ventilated patients, maintaining a constant inspired NO concentration despite changes in minute and tidal volumes may be problematic. Most pediatric ventilators pass a continuous gas stream around the ventilator system. Ventilation is achieved by altering the pressure and is independent of the flow rate of the gas stream. Thus, when a fixed concentration of NO is added to the inspiratory limb, the delivered concentration of NO will be constant and independent of changes in minute ventilation. In adult ventilators, flow occurs only during inspiration and changes with alterations in minute ventilation and tidal volume. Systems have been developed to ensure a constant concentration of inhaled NO when using a Siemans 900C ventilator in adults.71-73

The concentration of NO and NO2 should be monitored continuously. Available methods include chemiluminescence and electrochemical methods. Chemiluminescence may be the most accurate method of measuring NO concentration, but it is expensive and cumbersome. Electrochemical analyzers are inexpensive and more suitable for routine clinical use in most instances.

Conclusions

Inhaled NO is a selective pulmonary vasodilator in adult and pediatric patients. There is growing evidence that it may be a useful therapeutic agent in the treatment of pulmonary hypertension and hypoxemia from a variety of causes. Areas of greatest benefit may involve treatment of PPHN and ARDS. While inhaled NO exerts acute beneficial effects, it is unclear if there are long-term beneficial effects. Multicenter trials are currently underway to determine if inhaled NO decreases mortality from PPHN or decreases morbidity associated with ARDS.

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